Heat shock Protein 70 gene polymorphism and Hospital outcomes in Patients with acute pancreatitis.

A dissertation submitted in partial fulfilment of the requirements for DM (Branch IV, Gastroenterology) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in August 2013.

Certificate

This is to certify that this dissertation entitled **"HEAT SHOCK PROTEIN 70 GENE POLYMORPHISM AND HOSPITAL OUTCOMES IN PATIENTS WITH ACUTE PANCREATITIS"** is a bonafide work done by Dr. Unnikrishnan L.S. in partial fulfilment of the rules and regulations for DM (Branch IV – Gastroenterology) examination of The Tamil Nadu Dr MGR Medical University, to be held in August 2013.

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Introduction

Acute pancreatitis is defined as a process involving inflammation of pancreas, the surrounding tissues as well as distant organs [1]. Incidence of acute pancreatitis differ in different parts of the world, possibly due to the differnce in the consumption of alcohol in different places as well as difference in the incidence of gall stones in different parts of world. [2]. Previous studies reported the occurence of acute pancreatitis ranging from 4.9 to 35 per 1 lakh populations [3]. Severe disease was reported in about 20% of individuals and may be associated with mortality close to 20% [4].

There are varied aetiologies for acute pancreatitis. In one study Steer M L et al, found that in 45 percent of cases, cholelithiasis was the cause followed by ethanol in 35 percent ,rest in 10%. In about 10%, a specific cause could not be found and was grouped under idiopathic[5] . In India, the aetiological spectrum of mild pancreatitis included the following: alcoholism in 41.1%, gallstones in 23.5%, trauma in 17.6%, idiopathic in 11.7% and post-endoscopic retrograde cholangiopancreatography in 5.8%. [6].

Acute pancreatitis patients, usually present with pain abdomen and vomiting. Pain typically starts in epigastrium and may be radiating to the back also. Abdominal examination may reveal tenderness in the epigastrium. In mild cases, usually there will be an uneventful recovery and may require only few days of admission in hospital. In severe cases, pain may be severe with increase in heart rate, tachypnoea, decreased urine output and hypotension. There can be various signs on abdominal examination like cullens and Gray Turners signs. In severe cases death also can occur [7]. Such patients can be grouped as severe acute pancreatitis when they present with /develop organ failure and or with local complications such as fluid collections, necrosis, abscess, or pseudocyst [1].

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It is becoming clear that some combination of genetic mutation polymorphisms provides predisposition for severity of the "cytokine storm" following any insult that causes acute inflammation. In acute pancreatitis of any aetiology (e.g., alcohol, metabolic derangement, physiologic stress to acinar cells), this genetic polymorphic predisposition sets the stage for pancreatitis. Recently Heat Shock Protein 70-2 (HSP 70-2) gene has also been associated with pancreatic diseases, and so far various studies have shown conflicting results. So a definite role of this genetic polymorphism has not yet been confirmed in this disease [(7).]

The Heat shock proteins (HSPs) act as chaperones which is meant for cell protection from injury causing stimuli. In that way, there abnormal expression can lead to multiple diseases including various maignancies. There were previous studies which showed protective function of HSP 70 agnaist cell injuries and acinar cell necrosis of pancreas in animal models using knock-out and transgenic approach, as well as using standard methods of heat shock protein 70 (HSP70) induction such as thermal stress and arsenite administration[(8)] .

There are three members in HSP 70 gene family which was mapped and studied in detail in humans. They include HSP 70-1, HSP 70-2, and HSP 70-HOM, of which HSP 70-2 encodes the major heat inducible HSP70. Previous studies by Milner et al. identified polymorphism in HSP 70 gene, polymorphic A to G transition PstI site at position 1267 in HSP 70-2 coding regions[(9)]. Those who are homozygous for this specific HSP 70-2 G allele was shown to have reduced HSP70-2 mRNA expression [(10)], and it was also shown that this HSP70-2 –1267 A/G is associated with increased risk for various diseases and its poor outcomes. It was also shown that those having the above mentioned HSP 70-2 G alleles are at risk for developing acute severe pancreatitis [(11)].

HSP70 is also involved in the innate immune and inflammatory response and certain genotypes of HSP70 are associated with higher cytokine output in response to any inflammatory stimulus. So assessment of genotype may turn as an important tool for predicting prognosis and severity of diseases and for predicting the course of acute pancreatitis. Hence assessment of genotype may be used as an important tool to guide treatment and to identify population at risk for severe acute pancreatitis.

We proposed that polymorphisms in the Heat Shock Protein 70 gene may play a significant role in determining whether the illness manifests as a mild acute pancreatitis or as a severe acute pancreatitis, i.e. it may have a disease-modifying effect.

AIM

To determine whether there is any association between Heat Shock Protein 70 gene polymorphisms and severity of illness and hospital outcomes in patients with acute pancreatitis admitted to a tertiary care hospital.

Review of Literature

Definition

Acute pancreatitis is defined as a process involving inflammation of pancreas, the surrounding tissues as well as distant organs[(1)]. It can be caused by a variety of conditions and can lead to mild acute pancreatitis which is self limiting to severe life-threatening illness.

In 85% of cases with acute pancreatitis, it can be benign . In the rest 15 % of cases it can turn out to be sever, life threatening which requires admission in intensive care units and requiring mechanical ventillaton, dialysis and ionotropic supports. In acute pancreatitis, there is acute inflammation in pancreas with premature activation of pancreatic enzymes. In these cases there is pancreatic parenchymal destruction with activation of coagulation, kinin, complement and fibrinolytic cascades with increased release of cytokines and reactive oxygen metabolites. This in turn can leads to hypotension, respiratory and renal failures requiring dialysis and ventillatory supports. [(12)].

Incidence

The reported annual incidence of acute pancreatitis has ranged from 4.9 to 35 per 100,000 populations[(3)]. Recent increase in the incidence of acute pancreatitis was noted in many countries including Finland, England, Scotland and Germany. There was a recent increase in the incidence of acute pancreatitis to 31.8 per 1 lakh in 1985 from 9.4 per 1 lakh in 1968. Similar trend was noted in other countries like England and Denmark. This phenomenon was explained by the recent increased alcohol intake by the people from these countries as well as by the advancement in field of diagnostic imaging modalities [(13)] .

Aetiologies

The aetiologies of acute pancreatitis were due to alcoholism in 35.5%, gallstones in 22%, trauma in 20%, idiopathic in 13.3% and ERCP 8.8% in one study from Eastern India[14]. In one study from central India, the various causes attributed for the development of acute pancreatitis were gallstones in 48%, alcohol in 28%, and others in 24% of the patients [15]. In one study from Germany the reported incidences were cholelithiasis in 45% of cases, alcohol as the etiology in 35%, others in 10% and idiopathic in 10%[16] .

Physiology of pancreatic secretion

With stimulation by secretin the daily out put from the pancreas was found to be 1500 - 2000 ml of pancreatic fluid fluid and about 150 - 200 mmol HCO_3. Lipolytic, amylolytic and proteolytic enzymes were also secreted by the pancreas upon cholinergic stimulation. Enzymes for the proteolysis is secreted in a precursor inactive form. This has to be activated by trypsin. Trypsin is an activated form of enzyme which is produced by the conversion from inactive form, the trypsinogen with the help of enterokinase, an enzyme secreted from the mucosa of duodenum. Other proteolytic enzymes like chymotrypsinogen, proelastase, procarboxypeptidases and lipolytic and amylolytic enzymes are converted to their active form with the help of trypsin.

These enzyme precursors are stored in the zymogen granules. Also there are various antitrypsins like pancreatic secretory trypsin inhibitor, α_1-antitrypsin, α_2-macroglobulin . These above mechanisms protect the pancreas from the enzymatic digestion. When these

mechanisms fails then there will be premature activation of pancreatic proenzymes and there by leading to pancreatic parenchymal damage .

Pathogenesis of Acute Pancreatitis

The initial insult of these pancreatic premature activation of enzyme precursors is an abrupt increase in the calcium levels in the cytosol. This can lead to premature activation of these enzyme precursors[17]. This in turn leads to pancreatic parenchymal destruction with activation of coagulation, kinin, complement and fibrinolytic cascades with increased release of cytokines and reactive oxygen metabolites. These results in a massive release in the inflammatory cytokines like TNF-α, IL-1, IL-6, IL-8, platelet-activating factor along with reactive oxygen metabolites. The massive inflammatory response resulting from the above changes results in the systemic manifestations of acute pancreatitis. This in turn can leads to increased capillary permeability, hypotension, respiratory and renal failures requiring dialysis and ventillatory supports.

Role of Pancreatic enzymes in the genesis of Acute Pancreatitis

The raised intraductal pressure inside the pancreatic duct as a result of obstruction in the pancreatic duct due to stone, edema or spasm of the sphincter of oddi is termed as pancreatic duct hypertension. This can results in small pancreatic ductal rupture thereby causing extravasations of pancreatic enzymes into the parenchyma, leading to pancreatic injury .

Duodenopancreatic reflux can result in reflux entry of enterokinase into the pancreas from the duodenal lumen which can result in formation of trypsin, the activated form of enzyme which is produced from the inactive form, the trypsinogen. This reflux entry happens due to the sphincter incompetency secondary to the effect of alcohol, stone passage or result of

procedure / surgery. Other proteolytic enzymes like chymotrypsinogen, proelastase, procarboxypeptidases and lipolytic and amylolytic enzymes are converted to their active form with the help of this prematurely activated trypsin. This in turn leads to the deustruction of cell menbranes, edema and further pancreatic parenchymal damage.

Decreased apical exocytosis of pancreatic zymogens: There is decreased secretion from the apical side of zymogen granules in cases with acute pancreatitis where as the production inside the cell of these granules remains normal. As a result there is accumulation of these zymogens inside pancreatic cell. The proposed theory is that, these zymogen granules fuses with the membrane of lysozymes inside the cell, followed by activation of the trypsinogen by the cathepsin B, which leads to increased production of active trypsin thereby resulting in activation of other precursor enzymes and leading to further pancreatic parenchymal damage.
Hypersecretion : One of the rare causes for acute pancreatitis is the hyper secretion of pancreatic enzymes. This happen when there is increased muscarinic stimulation, which can occur in association with either poisioning with organophosphates or with scorpion enveommation[(12)].

Role of calcium

When there is some obstruction to the pancreatic duct, the pancreatic exocrine part changes its pattern to a calcium signalling pattern. It will result in premature activation of the pancreatic enzymes and there by leading to acute pancreatitis[11)]. Cholecystokinin and acetylcholine generates the calcium signal. The cholecystokinin can also stimulate the mitochondria. Usually the local cytosolic calcium will act only for a short time and the sustained elevated calcium level secondary to toxic cholecystokinin level may be the culprit behind the inflammatory states in acute pancreatitis. This toxic levels is also responsible for

the formation of to post-exocytic endocytic vaculoe formation. The pancreatic enzyme got activated in these vacuoles.

In those with alcohol related pancreatitis , the premature activation of trypsinogen can be explained through a calcium dependent mechanism. This happens through the non oxidative metabolites such as fatty acids ethyl esters and fatty acids itself[12]. Following activation of trypsinogen to trypsin, the rest of the enzymes also got activated leading to the inflammatory cascade in acute pancreatitis .

The main pathogenic mechanisms underlying an episode of acute pancreatitis classically involving the following acinar responses : first one is the accumulation of the vacuoles and the trypsinogen activation. Following the activation of the trypsinogen by the cathepsin B, which leads to increased production of active trypsin, there is activation of other precursor enzymes and leading to further pancreatic parenchymal damage.

The pathologically activated trypsin in the acinar cell can be degraded by the pancreatic zymogens, chymotrypsin C. The inactivating mutations in chymotrypsin C is also suggested as one of the cause that can increase the risk for chronic pancreatitis, mainly in those with increased alcohol consumption.

Acute pancreatitis is a dynamic disease with involvement of multiple systems, including the cardiovascular system, renal system, respiratory system, necrosis and infarction of the pancreas, and translocation of bacteria from gut as a resulting from gut injury. Vascular leak syndrome, which develops in cases with severe pancreatitis is responsible for the hemoconcentration, respiratory failures, renal failures and hypotension. Some of the autocrine peptides like angiopoietin 1 and 2 are responsible for increasing and decreasing the

endothelial permeability respectively. So the severity of the pancreatitis and persistent organ failure is related to the serum angiopoietin-2 levels. So organ failure can be predicted by an admission angiopoietin -2 levels.

Role of Genetic Factors in Pancreatitis

One of the rare forms of recurrent acute and chronic pancreatitis is the Hereditary pancreatitis (HP). The gene responsible for this was mapped to chromosome 7q35 using genome-wide genetic linkage analysis[18]. Later further gene sequencing of 7q35 chromosome region revealed a strong relation of c.365G > A (p.R122 H) mutation of the *PRSS1* gene which encodes cationic trypsinogen with HP. This mutation results in raised autocatalytic conversion of trypsinogen to the active trypsin and there by causing premature activation of intrapancreatic trypsinogen in vivo.

Patients who are homozygous for *SPINK1* N34S mutation are classicaly presents with features suggestive of chronic pancreatitis in early childhood. The exact mechanism underlying how this mutation leads to chronic pancreatitis is still un known. Some speculates that the reason behind, N34S being associated with decreased expression of *SPINK1* is due to to the haplotypes and intronic mutations associated with the N34S [19].

It was found in many studies that 30% of idiopathic chronic pancreatitis is associated with *CFTR* mutations. Mutations in CFTR are associated with high risk for chronic pancreatitis especially in those who are having two or more heterozygous mutations or one mutation in CFTR accompanied by mutations of *PRSS1* and *SPINK1* [20].

Systemic inflammation

Local injury in the setting of acute pancreatitis may proceed to a systemic inflammatory response syndrome (SIRS). SIRS is defined by 2 or more of the following criteria: pulse rate greater than 90 / min, respiratory rate above 20 per min or an arterial partial pressure of carbondioxide (PaCO2) of less than 32 mm Hg; temperature higher than 38degree C or less than 36 degree C; white cell count greater than 12,000 or less than 4000 cells / mm3.

In this acute pancreatitis setting, cytokine cascades activated by the pancreatic inflammation manifest clinically as the systemic inflammatory response syndrome (SIRS) and if the SIRS is persisting there is high risk for multiple organ dysfunction syndrome and even mortality. So presence of SIRS can be taken as an indicator of disease severity in cases with acute pancreatitis. In acute severe pancreatitis, there is an interplay between the pro- and anti-inflammatory response of cytokines in the cells and this will be present in the body for some time.

The neutrophils which are activated by cytokines infiltrates the organs like the liver, lung and GIT. The distant organ damage in severe pancreatitis can be explained by the effect of proteolytic enzymes that is releasing from neutrophils during the episode. This leads to injury of these vital organs and resulting in multiple vital organs dysfunction distant from the pancreas. The cytokines which are responsible for these injuries include TNF -alpha, interleukin- 1 (IL-1), interleukin-6 (IL-6) and interleukin-8 [(21)]. Apart from this complications in both sepsis and severe acute pancreatitis is mediated by endotoxins and other inflammatory mediators such as platelet activating factor and phospholipase A2.

Role of Genetic Polymorphisms In Systemic Inflammation

Heat Shock Proteins

Recently Heat Shock Protein 70-2 (HSP 70-2) gene has also been found to be associated with pancreatic diseases, and so far various studies have shown conflicting results. So a definite role of this genetic polymorphism has not yet been confirmed in this disease [(7).]

The Heat shock proteins (HSPs) act as chaperones which is meant for cell protection from injury causing stimuli. In that way, there abnormal expression can lead to multiple diseases including various maignancies. There were previous studies which showed protective function of HSP 70 agnaist cell injuries and acinar cell necrosis of pancreas in animal models using knock-out and transgenic approach, as well as using standard methods of heat shock protein 70 (HSP70) induction such as thermal stress and arsenite administration[(8)] . They are named based on their molecular weight, like, HSP70 refers to a family of these proteins with a molecular weight of 70 kilodaltons [(22).]

In 1962, Ritossa noted a typical puffing pattern in the chromosomes of Drosophila when induced by a metabolic inhibitor dinitrophenol[(23)]. This finally led to the identification of the stress proteins or heat-shock proteins (HSP).

Functions of Heat Shock Proteins

1. up regulation in stress

It was shown that the concentration of heat shock proteins was increased on exposure to different stressful environmental conditions.

2. Role as chaperones

An important function of heat shock proteins is its role as chaperones, that is it helps in the folding and establishment of proper shape of various proteins . This intracellular action helps in preventing the unnecessary aggregation of proteins. Through these properties of they helps in the protein transportation across the membranes [(24) .]

3. Role as House keeping

Heat Shock Proteins helps in house keeping actions inside the cells by taking all the old proteins to the proteosomes and helps in the proper establishment of the new proteins.

4. Role in Immunity

Heat Shock Protein 70 helps in binding of the antigens and carrying it to the immune system[25].

5. Role in Cardiovascular system

Heat Shock Protein 90 binds both soluble guanylate cyclase and endothelial nitric oxide synthase which are involved in vascular relaxation [26].

The major heat shock protein for the normal cellular homeostasis in humans is the HSP70. The HSPs has got both anti-inflammatory as well as the proinflammatory effects, in regulating the human health. These properties of heat shock proteins depends on what is the cell type, the context and the site, that is whether it is intracellular or extracellular location. The anti-inflammatory effects are ususally intracellular, and is by nuclear factor κB signalling inhibition. The cytokine production is ussually as a result of extracellular effects. The other extracellular effects being the induction of regulatory immune cells and reduced inflammation [27]. HSP70, although usually is intracellular, but can be released extracellularly also when the cells are stressed, especially in the setting of necrosis [28].

Studies have showed that the induction of heat shock proteins (HSPs) are up regulated in acute pancreatitis and also it showed a protective effect in experimental pancreatitis [29].

Certain genotypes of HSP70 are associated with higher output of cytokines in response to any inflammatory stimulus. There are three members in HSP 70 gene family which was mapped and studied in detail in humans. They include HSP 70-1, HSP 70-2, and HSP 70-HOM, of which HSP 70-2 encodes the major heat inducible HSP70.

A genetic polymorphism can be defined as a genetic variant that appears in at least 1% of population. We can exclude spontaneous mutations that might have occurred in and spread through the descendants of a single family by setting the cut-off of 1%.

The HSP gene polymorphism results in the defective HSP production with in the cell as well as imbalance in the inflammatory cytokines.

Previous studies by Milner et al. identified polymorphism in HSP 70 gene, polymorphic A to G transition PstI site at position 1267 in HSP 70-2 coding regions[9]. Those who are homozygous for this specific HSP 70-2 G allele was shown to have reduced HSP70-2 mRNA expression [10], and it was also shown that this HSP70-2 –1267 A/G is associated with increased risk for various diseases and its poor outcomes [32, 33, and 34]. It was also shown that those having the above mentioned HSP 70-2 G alleles are at risk for developing acute severe pancreatitis [11].

It was found in many studies that polymorphism in HSPA1L gene is related to reduced levels of inducible HSP70 in monocytes and lymphocytes. The low levels are correlated much with the the CC genotype than the TT genotype [36]. In the same study they could not find any specific association between polymorphism in HSPA1B gene and intracellular HSP70 response. In another study cardiac failure was found to have association with HSPA1BG allele[37]. Diabetic ketoacidosis is another health problem that is related to increased

extracellular levels of HSP70 [38], but its relationship to the HSPA1B or HSPA1L genotype is still unknown. Another health issue related to genotypes HSPA1B AG or HSPA1LCT is severe multiple trauma. In those patients with multiple severe trauma and is having the above genotypes was found to have a significantly higher plasma concentrations of TNF-α and IL-6 than those with GG or TT genotypes [39]. Also it has been shown in one previous study that HSPA1 B AG genotype was significantly associated with a more severe local disease in patients with diabetic foot, amputation rate and longer hospital stay than GG genotype [40].

It was demonstrated that there is a strong association between rs1061581, rs1043618 and rs1008438 polymorphisms with high altitude associated pulmonary edema [41]. Another study demonstrated an association between single nucleotide polymorphism (SNP) rs2227956 in HSP 70-hom, rs1043618, rs1061581 and noice induced hearing loss [42].

It was found in previous studies that there is a high risk that patient can go for a severe course of acute pancreatitis, if they have HSP70-2 G and the TNF-[alpha] – 308 A alleles . So assessment of genotype may turn as an important tool for predicting prognosis and severity of diseases and for predicting the course of acute pancreatitis. Hence assessment of genotype may be used as an important tool to guide treatment and to identify population at risk for severe acute pancreatitis.

It is getting more and more clearer that the various genetic polymorphism combinations predispose to the occurrence of acute pancreatitis. On the top of that if one or more risk factor is added such as metabolic, alcohol or physiological stress etc, it will predispose to acute pancreatitis.

Some earlier studies have shown the dual role of HSP 70 in various pancreatic diseases. The protective role of HSP 70 is that it protects from cellular injury as well as from the necrosis of the acinar cells [8].

There were three studies which assess various polymorphisms in cases with pancreatic diseases, of which two were carried out in cases with acute pancreatitis [43, 44] and one in cases with chronic pancreatitis [45]. While one of the studies evaluated the role of three specific polymorphisms (HSP 70-2, TNF-alpha, and CD14 genes) in determining the susceptibility to severe acute pancreatitis of different aetiologies, the second study assessed the role of CD14, TNF and HSPA1B gene polymorphisms to see for the susceptibility to acute alcohol induced pancreatitis. The third one evaluated the role of MCP 1 and HSP 70-2 genes and its susceptibility to alcoholic induced chronic pancreatitis.

In one recently published Indian study, mutant allele of HSP 70-2 gene (G allele) was assessed. This was assessed in cases with acute pancreatitis, chronic pancreatitis and pancreatic carcinoma. In this study, patients with acute pancreatitis with various complications like acute fluid collection, ascites, pseudocyst, pleural effusion, any local complication, organ failure such as gastrointestinal bleed, respiratory failure, renal failure, shock and sepsis were studied for their association with HSP 70 gene polymorphism. However, there could not find any significant association noted in the genotype distribution and development of any of such complications.

The possible explanations for the lack of such associations could be due to 1) larger sample size that is required for genetic association studies 2) the different ethnic composition of study population when compared to other studies, in which the polymorphism distribution

was not even comparable among control population 3) the different haplotypes in chromosome 6 such as TNF alpha and beta, the complement components C2, C4 and the Bf, the enzyme 21 hydroxylase, etc, which are very much in close proximity with HSP 70-2 genes and can also have an impact on the disease severity and for predisposition to the development of various complications through the effect of linkage disequilibrium, via promoter, modifier or the suppressor effect.

This study also showed the presence of significantly higher frequency of HSP 70-2 gene mutant allele (G allele) in cases with acute pancreatitis and also in pancreatic carcinoma cases when compared with the control population. The frequency of mutant allele was higher in all the three diseased groups when compared with the control group. There was no association noted between this polymorphism and disease severity as well as with the complications. However, in cases with chronic pancreatitis though the AG and GG alleles were more common, these differences did not reach statistical significance [46].

TNF, CD 14 and IL-10 gene Polymorphisms

It was also suggested that there is an association between the risk for pancreatitis with alcohol as the etiology and the severity of the disease during its course with the TNF, *CD14* and *IL-10* inflammatory gene polymorphisms. So assessment of genotype may turn as an important tool for predicting prognosis and severity of diseases and for predicting the course of acute pancreatitis. Hence assessment of genotype may be used as an important tool to guide treatment and to identify population at risk for severe acute pancreatitis.

Pathogenesis of systemic and local complications in acute pancreatitis

In the initial stages there is precursor enzyme activation which results in damage to the pancreatic parenchyma, interstium and vascular endothelium. In various studies, it was demonstrated that there is circulatory changes at the microscopic level, vasoconstriction, stasis of the blood at the level of capillaries and finally leading to ischemic injury [47]. These further can be damaged through means of ischemia –reperfusion injury. Also it can results in edematous pancreatic parenchyma formation and the so called interstitial pancreatitis. [48]

In some previous studies using animal models and also in humans, it was shown using Indium-111 tagged leukocytes that there is significant infiltration of the pancreatic acinar cells with macrophages and neutrophils in animal and human models of pancreatitis [49]. The recruitment of the inflammatory cells into these tissues is largely influenced by complement activation and by subsequent C5a release.

These infiltrated neutrophils and macrophages in turn will result in the release of various proteolytic enzymes, lipolytic enzymes, reactive oxygen metabolites. The proinflammatory cytokines such as interleukins (IL) 1, 6, and 8, the tumor necrosis factor (TNF), and arachdonic acid metabolites such as prostaglandins, platelet-activating factor, and leukotrienes were also released through these process. In effect, the activation of these cytokines is also extended to distant sites apart from the pancreatic and peripancretic tissue, as evidenced by detection of significant up-regulation of TNF-a mRNA in the splenic mononuclear cells in rat models following induction of acute pancreatitis [50]. These local and the systemic inflammatory substances over ride the protecting ability of the antioxidant mechanisms within the body. Pancreatic microcirculation is affected through the above mechanisms and can results in increased vascular permeability, thrombosis, hemorrhage, and

finally pancreatic necrosis. The above mentioned responses in its severe form can lead to systemic insult and to the development of SIRS. The various systemic complications, like acute respiratory distress syndrome (ARDS), pleural effusions, hypotension , failure of the kidneys and myocardial dysfunction can be as a result of these mechanisms (51). The ARDS can also explained by the increased release of activated phospholipase A or called lecithinase, that can digest lecithin, which is considered to be a a major component of surfactant.

Lung injury in cases with severe pancreatitis can also be mediated by up-regulation of adhesion molecules. In acute pancreatitis there is increased inflammatory infiltrate in the lung tissue, followed by release of cytokines resulting in up-regulation of P- and E selectin. The expression of these selectins correlates with the increased infiltration of CD18 - positive cells and neutrophil sequestration in the lung tissue. These are all well correlated with histologic pulmonary injury and increased activity of myeloperoxidase in the lung tissue. Lung injury also has been associated with the over expression of VCAM 1 [(52)] and increased expression of P-selectin through a free radical dependent mechanism which is generated by the damaged pancreas. In addition, the trypsin generated complement activation was shown to participate in up regulation of the Mac-1 and shedding of the L-selectin on neutrophils in acute pancreatitis [(53).]

Myocardial depression and shock can well be explained by the hyper catabolic state and disturbed peripheral microcirculation with resulting reduced tone of the vessels and thereby leads to reduced tissue oxygenation[(54)].

Acute kidney injury in cases with acute pancreatitis has been attributed to hypovolemia and hypotension. Various metabolic complications such as diabetic ketoacidosis, hyperglycemia, hyperlipidemia, hypoglycemia and hypocalcemia have also been described. The pathogenesis of hypocalcemia is multifactorial and it includes calcium soap formation, binding of calcium by the free fatty acid–albumin complexes, hormonal imbalances such as parathormone, calcitonin, glucagon), and the intracellular translocation of calcium.

During the natural course of acute pancreatitis the permeability of the gut is compromised, leading to the translocation of bacteria, which can result in septicaemia . The breach in gut barrier is thought to be secondary to the pancreatitis-induced gut arteriovenous shunting and also as a consequence of ischemia caused by hypovolemia [(55)]. Isolation of common enteric organisms from the pancreatic infection supports the notion that these organisms have translocated from the gastrointestinal tract.

In about 30% of cases with severe acute pancreatitis bacterial sepsis occurs in the pancreatic and the peripancreatic tissues . Infection carries the potential of a multiorgan failure and its consequences, which could be fatal event. Bacterial translocation and the endotoxemia, were proposed as mechanisms behind the violent cytokine response observed in acute pancreatitis.

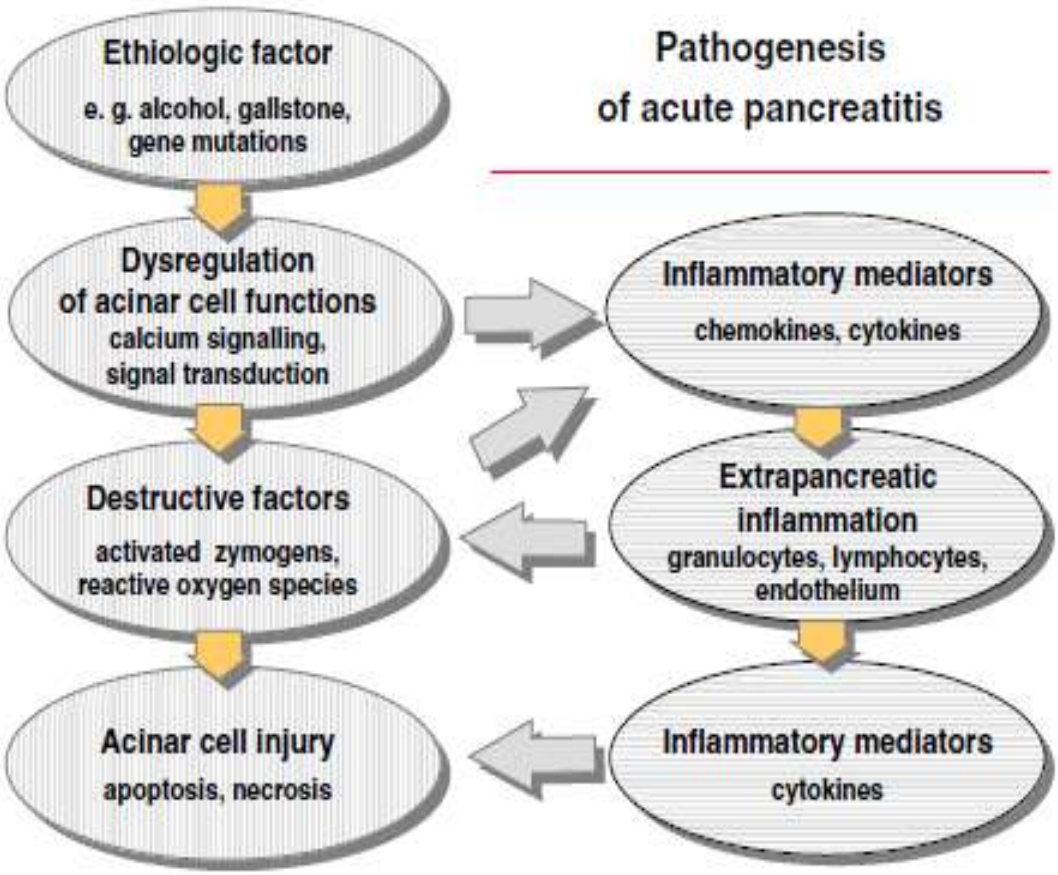


Fig 1: Various events in acute pancreatitis . With the initiation of pathophysiological changes inside acinar cell (left side sequence), signal metabolites induces an extra pancreatic inflammatory response (right side sequence). These processes interact with each other and contribute to the progression of the disease.

CLINICAL FEATURES

Acute pancreatitis patients, usually present with pain abdomen and vomiting. In about 90% of cases nausea and vomiting can be present.

Pain typically starts in epigastrium and may be radiating to the back . Abdominal examination may reveal tenderness in the epigastrium. In mild cases, usually there will be an uneventful recovery and may require only few days of admission in hospital. In severe cases, pain may be severe with increase in heart rate, tachypnoea, decreased urine output and

hypotension.There can be various signs on abdominal examination like Cullens and Gray Turners signs. In severe cases death also can occur [7]. Such patients can be grouped as severe acute pancreatitis when they present with /develop organ failure and or with local complications such as fluid collections, necrosis, abscess, or pseudocyst [1].

Respiratory signs such as pleural effusions especially on the left with or without left sided basal lung collapse, wheezing, and sometimes with basal crepitations. Cullen' s sign is a faint blue discolouration noted around the umbilicus (due to haemoperitoneum) and Grey - Turner's sign is a a blue red purple or brown discolouration of the flanks (due to retroperitoneal haemorrhage) may observed after 48 hr. Sometimes, erythematous skin nodules due to subcutaneous fat necrosis can also be found.

The differentials for acute pancreatitis include perforation peritonitis, intestinal ischemia , intestinal obstruction, renal or biliary colic, acute myocardial infarction etc. .

SEVERITY OF ACUTE PANCREATITIS

Acute pancreatitis can be either mild (85% cases) or can be severe (15% cases). Those acute pancreatitis which is associated with organ failure and or associated with local complications such as necrosis, abscess or pseudocyst and is often characterised by an extensive peripancreatic and intrapancreatic fat necrosis, haemorrhage and parenchymal necrosisis is grouped under severe..

Severe Acute Pancreatitis:

Acute pancreatitis which is associated with organ failure and /or local complications, such as necrosis, abscess, or pseudocyst is grouped as severe acute pancreatitis [1].

Acute mild Pancreatitis:

Those acute pancreatitis which is associated with minimal or transient organ dysfunction, leading to an uneventful recovery, and which lacks the described features of severe acute pancreatitis is grouped as acute mild pancreatitis [(1)].

Acute Fluid Collections:

It is the collection of the fluid which occurs early in the course of acute pancreatitis, and is located in or around the pancreas, which lacks a wall of granulation or fibrous tissue [(1)].

Pancreatic Necrosis

These are diffusely or focally affected well marginated zones of non enhancing pancreatic parenchyma which is nonviable, larger than 3 cm or involve more than 30% of the area of the pancreas, which is typically associated with peripancreatic fat necrosis [(1)].

Acute Pseudocyst:

A pseudocyst is a collection of pancreatic secretions which arises as a result of acute pancreatitis, pancreatic trauma, or chronic pancreatitis and is enclosed by a wall of fibrous or granulation tissue [(1)].

Pancreatic Abscess:

It is a well defined circumscribed collection of pus, with little or no pancreatic necrosis.

Usually it occurs in close proximity to the pancreas, and arises as a result of acute pancreatitis or pancreatic trauma [(1)].

Organ failure:

Organ failure comprise hypotension with systolic blood pressure < 90 mm Hg, pulmonary insufficiency ith a pulmonary arterial oxygen saturation of 60 mm Hg or less, kidney injury with a creatinine > 2 mg/dl after proper rehydration, or gastrointestinal bleeding (more than 500 ml/24 hours) [(1)].

The imporant other systemic complications are disseminated intravascular coagulation (platelet count of less than 1 lakh , fibrinogen of less than 1.0 g/L, and fibrin degradation split products of more than 80 pg/mL) or severe metabolic disturbances such as hypocalcemia (calcium level less than or equal to 7.5 mg/dL) [(1)].

Most of severe acute pancreatitis mortality is associated with the organ failure. In the early stages, organ failure is resulting from the inflammatory mediators released by systemic inflammatory response syndrome even if there is no infection. In the septic phase, organ failure occurs because of the sepsis. So organ failure is common in the genesis of severe acute pancreatitis. Previous studies showed that in severe acute pancreatitis, organ failure occurred in about 72-90.3 %, with one organ failure in 24.7-37 % of cases, multiple organ failure in about 35- 65.6 %. Respiratory failure is the most common single organ failure reported (39.1-63 %), followed by the cardiovascular failure (23-37.7 %), then liver failure (20.7 %), and followed by acute kindney injury (8.5-13 %) [(56)]. Previous studies also showed the mortality rate was 45 % in patients with multiple organ failure, and was 11 % in single organ failure group [(57).]

If there is a failure to improve in the condition of patient within 48 - 72 hr of supportive treatment, dynamic contrast enhanced CT of the abdomen should be taken to determine the severity of the disease.

Several prognostic scoring systems have been suggested to assess the severity of pancreatitis. The Ranson scoring system uses series of 11 prognostic signs, where severe acute pancreatitis is labelled if three or more criteria is present. A score of 10 or more during the first 48 hours of onset of symptoms while using the APACHE II criteria, indicates severe acute

pancreatitis. Balthazar score predicts severity of acute pancreatitis based on the abdominal CT appearances of pancreas which includes the presence or absence of pancreatic necrosis. The biochemical markers such as C-reactive protein, pancreatitis-associated peptide, neutrophil elastase, interleukins 1, 6, 8, 10 and soluble TNF receptors and urinary trypsinogen activation peptide can be used to assess severity of acute pancreatitis [(58)]. In another study they concluded that a the peak level of plasma C-reactive protein peak of more than 210 mg/L on day 2 - 4 or more than 120 mg/L at day 7 was as predictive as in any other multiple scoring systems [(59).]

Another scoring system used was Simplified Glasgow Score which we have used in our study. In this score of more than 2 is categorised as severe.

Variable include:

Age> 55 years

PaO2 < 60 mm Hg

WBC > 15,000 / mm3

Ca 2+ (uncorrected <8 mg %

Urea >45 mg %

Albumin <3.2 g %

For cases with acute pancreatitis, there is no specific treatment. These cases requires aggressive supportive management. This helps in reducing pancreatic secretion through reducing enteric stimulation. Other supportive treatments include administering of fluid, correction of electolytes and to provide relief from pain.

We proposed that polymorphisms in the Heat Shock Protein 70 gene may play a significant role in determining whether the illness manifests as a mild acute pancreatitis or as a severe acute pancreatitis, i.e. it may have a disease-modifying effect. So assessment of genotype may turn as an important tool for predicting prognosis, severity of diseases and for predicting the course of acute pancreatitis. Therefore, genotype assessments may also be used to guide treatment or to identify populations at risk for developing severe acute pancreatitis.

METHODS

Study design

This was a cross sectional study performed in the Christian Medical College, Vellore.

Inclusion criteria

Cases of acute pancreatitis the diagnosis of which was made on basis of history and investigations, including radiological evidence of acute pancreatitis and laboratory evidence of serum amylase greater than 3 times upper limit of normal

Exclusion criteria

Cases with evidence of chronic pancreatitis/tumours (ductal dilatation, ductal or Parenchymal calcification or pancreatic mass).

Patient or relative not willing to give written informed consent.

Study setting and Population:

The study was conducted in the department of Gastrointestinal Sciences in CMC Hospital, Vellore from February 2011 - Dec 2012. Data were collected from the patients with the diagnosis of acute pancreatitis of various aetiologies. They were recruited from the gastroenterology ward and also from the emergency services. They all had met the diagnostic criteria for acute pancreatitis, and also the inclusion and exclusion criteria. Purpose of the study was explained to these patients and an informed consent was taken. Adequate venous blood samples were then taken for further investigations. In the case of a few patients who were first admitted in another hospital and then transferred here the laboratory parameters in the first few days that were needed to calculate some scores (eg.SGS) of initial days of the disease of these patients were obtained from their outside hospital reports . In cases with diagnostic confusions or in cases with suspected complications, further investigations like

computed tomography was taken. No additional clinical laboratory tests were performed for the study other than those dictated for clinical care.

Informed Consent Process

Those patients who met the criteria were informed about the background and purpose of the study and they were invited to participate. If they were willing to participate, then written consent was obtained from the patient as per consent form appended.

Ethics Committee review

The Human Ethics Committee of CMC Vellore reviewed and approved the proposal and consent forms.

Study Monitoring

The study was an investigator-initiated study conducted in Christian Medical College, Vellore. The candidate conducting this study personally ensured the entry criteria of the patient and collected the relevant clinical and laboratory data from the patient. Consecutive patients were enrolled, subject to consenting. The molecular biology testing was performed in a research laboratory attached to the department by a specialist in this area .The clinical investigator was blinded to the genotype analysis, while the molecular biologist was blinded to the clinical data.

Methods of the Study

This study was conducted at Christian Medical College Vellore, Tamilnadu. Relevant clinical and laboratory data were collected from the patients by the medical officer in charge of the

study, once they received the informed consent after ensuring entry criteria. No additional tests were performed for disease categorisation other than those dictated for clinical care.

Sample size

From previous studies we determined that the inflammatory HSPA1B AG genotype was present in approximately half of our population [40]. The hypothesis was that this single nucleotide polymorphism (or other SNPs in the same gene) may have a 'modifier' effect on the course of acute pancreatitis. Therefore we expected that 50% of patients with acute pancreatitis would also have this inflammatory genotype. We have assumed that one third of patients with acute pancreatitis would have acute severe pancreatitis and two thirds would have acute mild pancreatitis. Assuming a relative risk of 3 for the development of severe pancreatitis in someone with an inflammatory genotype compared to a non-inflammatory genotype, we calculated the sample size of 124 patients to disprove the null hypothesis with a study power of 80% and type I error of 0.05.

The patients were those who were admitted to Gastroenterology ward or to the emergency ward with a diagnosis of acute pancreatitis were included. The following definitions were used in the study.

Severe Acute Pancreatitis:

Acute pancreatitis which is associated with organ failure and /or local complications, such as necrosis, abscess, or pseudocyst is grouped as severe acute pancreatitis [1].

Acute mild Pancreatitis:

Those acute pancreatitis which is associated with minimal or transient organ dysfunction, leading to an uneventful recovery, and which lacks the described features of severe acute pancreatitis is grouped as acute mild pancreatitis [(1)].

Acute Fluid Collections:

It is the collection of the fluid which occurs early in the course of acute pancreatitis, and is located in or around the pancreas, which lacks a wall of granulation or fibrous tissue [(1)].

Pancreatic Necrosis

These are diffusely or focally affected well marginated zones of non enhancing pancreatic parenchyma which is nonviable, larger than 3 cm or involve more than 30% of the area of the pancreas, which is typically associated with peripancreatic fat necrosis [(1)].

Acute Pseudocyst:

A pseudocyst is a collection of pancreatic secretions which arises as a result of acute pancreatitis, pancreatic trauma, or chronic pancreatitis and is enclosed by a wall of fibrous or granulation tissue [(1)].

Pancreatic Abscess:

It is a well defined circumscribed collection of pus, with little or no pancreatic necrosis.

Usually it occurs in close proximity to the pancreas, and arises as a result of acute pancreatitis or pancreatic trauma [(1)].

Organ failure:

Organ failure comprise hypotension with systolic blood pressure < 90 mm Hg, pulmonary insufficiency ith a pulmonary arterial oxygen saturation of 60 mm Hg or less, kidney injury with a creatinine > 2 mg/dl after proper rehydration, or gastrointestinal bleeding (more than 500 ml/24 hours) [(1)].

The imporant other systemic complications are disseminated intravascular coagulation (plateletcount of less than 1 lakh , fibrinogen of less than 1.0 g/L; and fibrin degradation split products of more than 80 pg/mL) or severe metabolic disturbances sucha as hypocalcemia (calcium level less than or equal to 7.5 mg/dL) [(1)].

Relevant clinical and laboratory data were collected from the patients by a medical officer in charge of the study once they received the informed consent after ensuring entry criteria.

9 ml of venous blood samples were collected in EDTA coated vacutainer tubes after obtaining informed written consent. Genomic DNA was isolated using standard salting out procedure. Genomic DNA from mononuclear cells in blood was extracted by phenol–chloroform extraction and kept −20°C for storage. Appropriate primers and restriction enzymes were used to genotype the HSPA1B A1538G, HSPA1L C2437T, rs1008438 and rs1043618 loci.

The HSP70 polymorphisms rs1061581 and rs2227956 were detected by PCR-RFLP method and rs1008438 and rs1043618 were detected by allele-specific PCR. The PCR reactions were of 20 µl volume and each reaction mix contained 1x taq DNA polymerase master mix Red (Ampliqon), 250nM of forward and reverse primers (Sigma genosys).

The thermal cycling protocol for rs1061581, rs2227956, rs1008438, and rs1043618 comprised of initial denaturation at 95°C for 5 min, cycle denaturation at 94°C for 30 sec, annealing temperature at 58°C and 62°C for 30 sec, extension at 72°C for 30 sec, and the cycle was repeated for 34 more times, final extension at 72°C for 5 min. The PCR products were checked for amplification by resolving on 2% agarose gel electrophoresis and checked with UV transilluminator (Vilbert Lourmat).

Then the amplified samples were digested with 2 units of restriction enzymes, PstI and NcoI (MBI Fermentas) respectively for rs1061581 and rs2227956 analysis at 37°C for 16 hours. The digested PCR products were resolved on 2% agarose gel electrophoresis and the gel patterns were documented using a gel documentation system (Vilbert Lourmat, France).

The genotypes were assigned for the PCR-RFLP analysis as given in the table.

SNP	Forward primer	Reverse primer	Product size	Restriction enzyme	Restriction fragments
rs1061581	CATCGACTTCTACACGTCCA	CAAAGTCCTTGAGTCCCAAC	1117	Pst1	AA -1117 GG – 936, 181
rs2227956	GATCCAGGTGTATGAGGG	GTAACTTAGATTCAGGTCTGG	705	Nco1	CC – 705 TT – 550, 155
rs1008438	CAGGACGGGAGGCGAAAC CAGGACGGGAGGCGAAAA	CACAGGTTCGCTCTGGGAA	219	-	-
rs1043618	GCTCGGTGATTGGCTCAGAA	CTGCTCTCTGTCGGCTCG CTGCTCTCTGTCGGCTCC	282	-	-

Statistical methods:

The data of the present study were recorded manually and into the computer and after its proper validation, checked for error, coding & decoding were compiled and analyzed using the software SPSS 11.5 for windows. Categorical data was compared using the Pearson Chi

square test, while continuous data was compared using two-tailed independent t tests. All the continuous variables were expressed as mean ± standard deviation.

Patients who were discharged against medical advice were discharged in moribund condition. For purpose of statistical analysis they were clubbed with those who died. In acute pancreatitis we considered that HSP gene 70 polymorphism will play as a modifier role rather than a causative role in the natural history of acute pancreatitis.

Apart from seeing the relationship between polymorphism with severity of pancreatitis, we also looked into the possible association between HSP 70 gene polymorphism and occurrence of organ failure, length of hospital stay including the duration of Intensive Care Unit stay and mortality associated with this disease.

RESULTS

Blood samples and relevant clinical data were collected from 127 patients admitted in the Gastroenterology ward with acute pancreatitis. Genetic analysis for the HSP 70 single nucleotide polymorphisms under study was performed only in 121 patients as there was a failure in DNA amplification process in 6 samples. Of the 127 patients, 61 were mild and 66 were severe. The baseline demographic data of the patients enrolled in this study were tabulated and given below

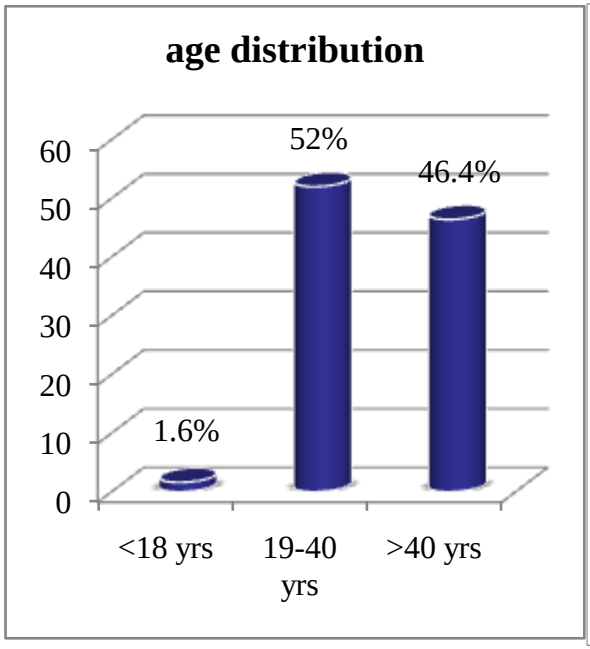
Table 1. General characteristics of the patients who were enrolled in the study. Some values shown are actual numbers while the others are mean ± SD.

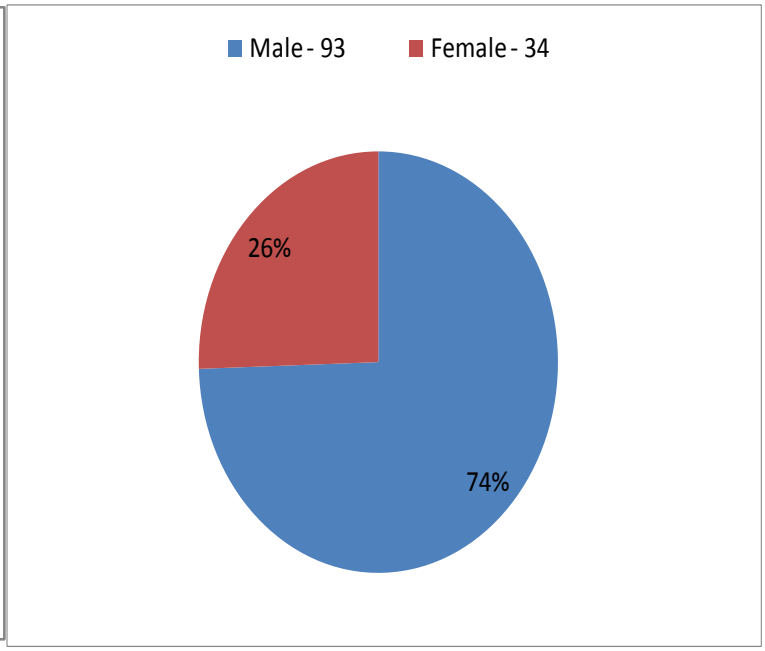
Particulars	Total	Mild	Severe
Total cases	127	61	66
Age(years)	40.17 ± 13.12	39.82 ± 12.30	40.50 ± 13.94
Male : Female	2.7 :1	2.1:1	3.64:1
SGS score	1.96 ± 1.90	0.62 ± 0.68	3.23 ± 1.80
CRP(mg/L)	181.99 ± 63.374	212.51 ± 90.74	152.88 ± 59.76
Amylase (U/L)	1004.92 ± 1055.39	1061.50 ± 1092.61	962.45 ± 1028.06
Lipase(U/L)	1938.62 ± 2516.68	2062.98 ± 2489.17	1820 ± 2556.28
PCV (%)	47.37 ± 39.88	45.86 ± 41.11	48.79 ± 38.92
Hospital stay (days)	11.81 ± 16.48	4.98 ± 2.73	18.32 ± 20.95
ICU stay (days)	3.24 ± 8.04	0.08 ± 0.45	6.26 ± 10.39

The mean age of patients participated in the study was 40.17 ± 13.12 years. The mean age of patients in mild and severe group was 39.82 ± 12.30 and 40.50 ± 13.94 respectively. The male female ratio was 2.7:1, 2.1:1, and 3.64:1 respectively for the total patients group, mild and severe group. The mean simplified glasgow score was 1.96 ± 1.90, 0.62 ± 0.68 and 3.23 ±

1.80 for total, mild and severe pancreatitis group. The mean CRP was181.99 ± 63.374, 212.51 ± 90.774 and 152.88 ± 59.76 for the the above respective groups. The mean amylase for the above group was 1004.92 ± 1055.39, 1061.50 ± 1092.61 and 962.45 ± 1028.06. The mean lipase was 1938.62 ± 2516.68, 45.86 ± 41.11 and 1820 ± 2556.28 for total group, mild and severe group respectively. Mean PCV were 47.37 ± 39.88, 45.86 ± 41.11 and 48.79 ± 38.92 for the above three groups. The mean total hospital stay for total group, mild and severe group was 11.81 ± 16.48, 4.98 ± 2.73 and 18.32 ± 20.95 respectively. The mean number of ICU stay was 3.24 ± 8.04, 0.08 ± 0.45 and 6.26 ± 10.39 days respectively.

Fig :1 showing Age and Sex distribution

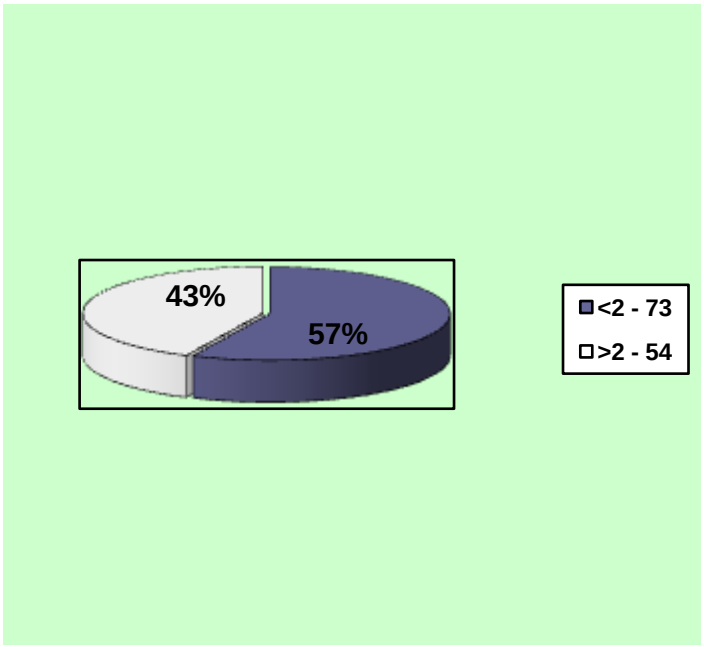


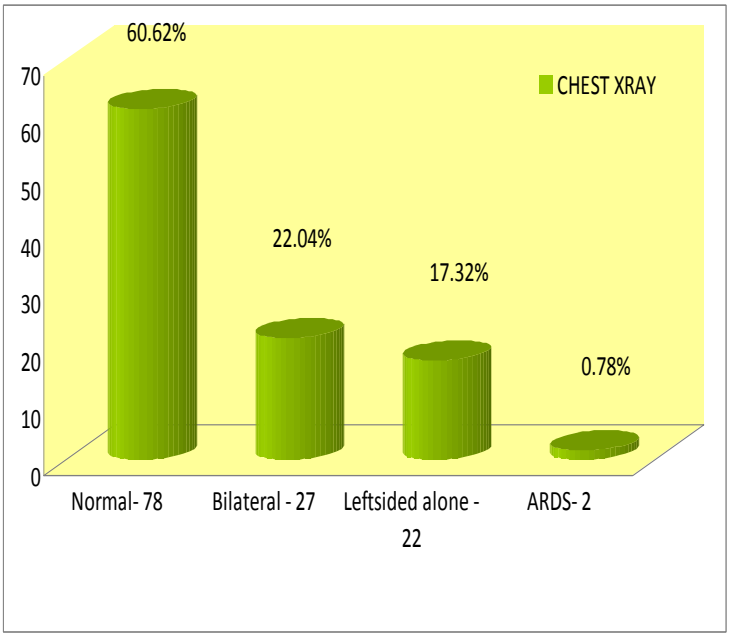


Of the total 127, 93 /127 (74%) were male and 34/127 (26%) were females.

Fig :2 Disease severity and chest x-ray findings

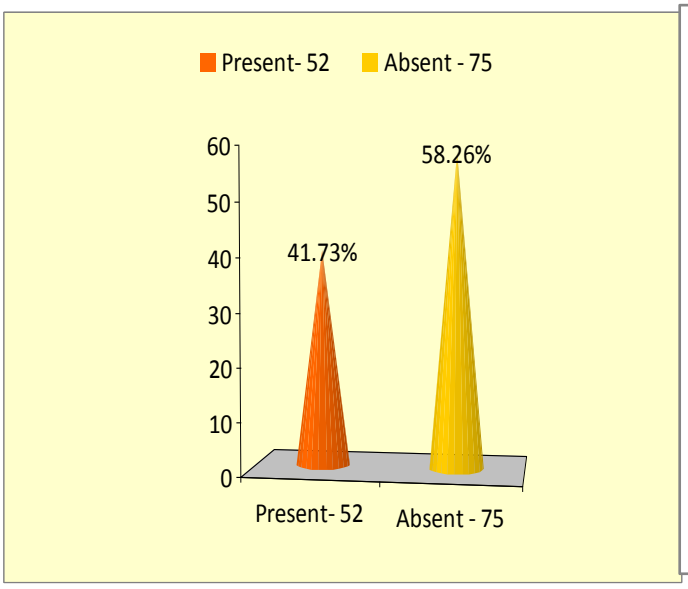
Simplified Glasgow Scoring **Chest X - ray findings**

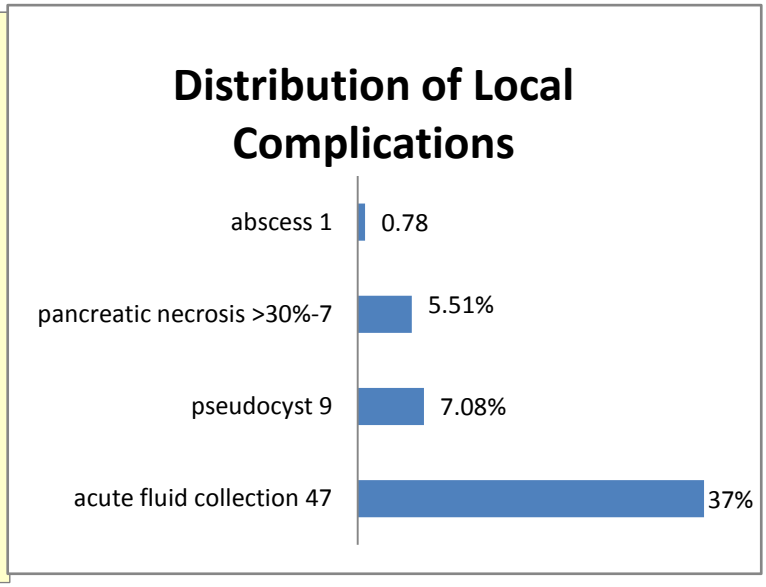




73 /127 (57%) patients had an SGS < 2 and 54 /127 (43%) had SGS > 2. 60.62% had normal chest xray, 22.07% had bilateral effusion, and 17.32 % had left sided alone. 2/127 (0.78%) had ARDS features on Xray at time of admission

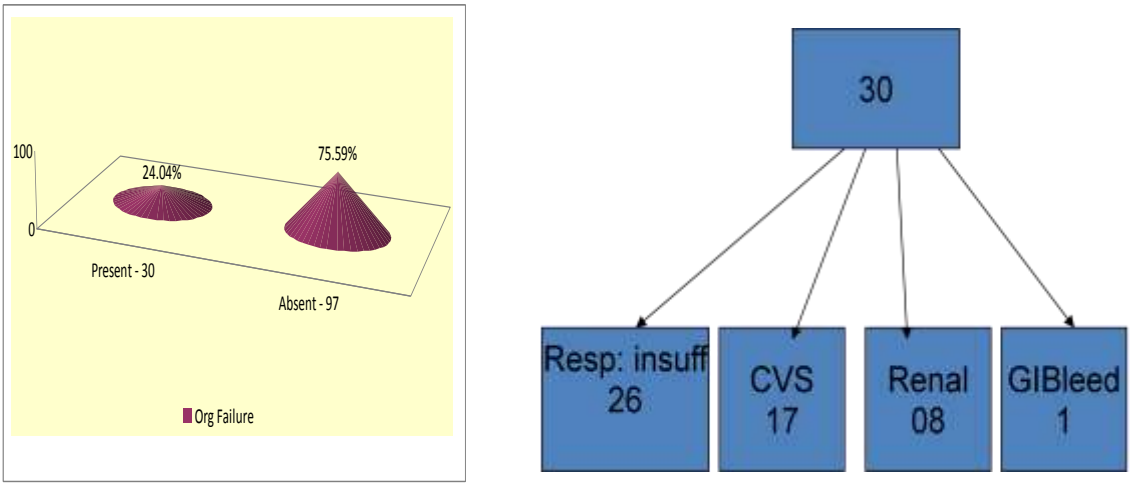
Fig 3: Showing the Local complications





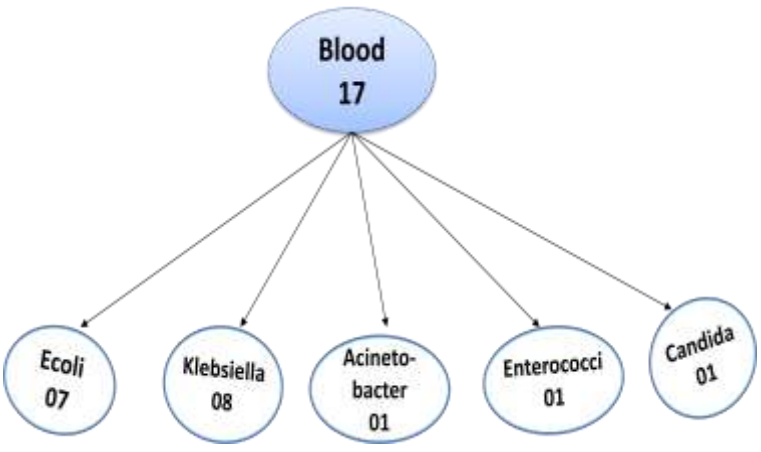
52/127 (41.73%) had local complications. Acute fluid collection in 37 %(47/127), pseudocyst in 7.08 %(9/127), pancreatic necrosis more than 30 % in 7/127(5.51%) and 0.7%(1/127) had abscess collection.

Fig 4: showing organ failure and its distribution pattern



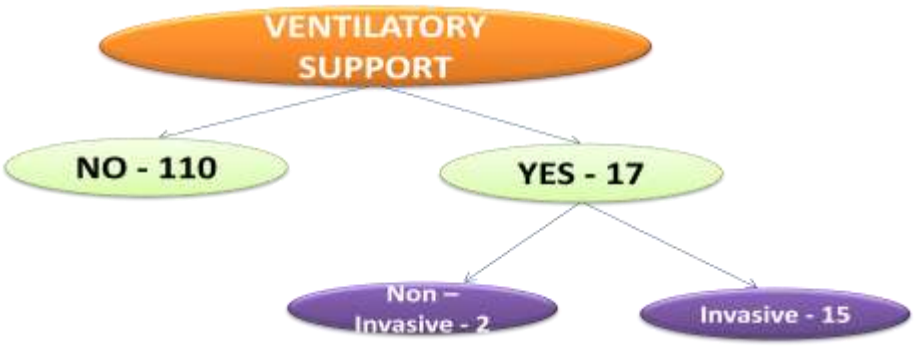
30/127 had organ failure (24.04%) of which 25 had respiratory complications, 14 had cardiovascular, 08 had renal, and 01 had GI bleed related complications. 50% (15 / 30) of patients who had organ failure had multiple organ failure.

Fig 5: The pattern of infection in culture positive acute pancreatitis patients



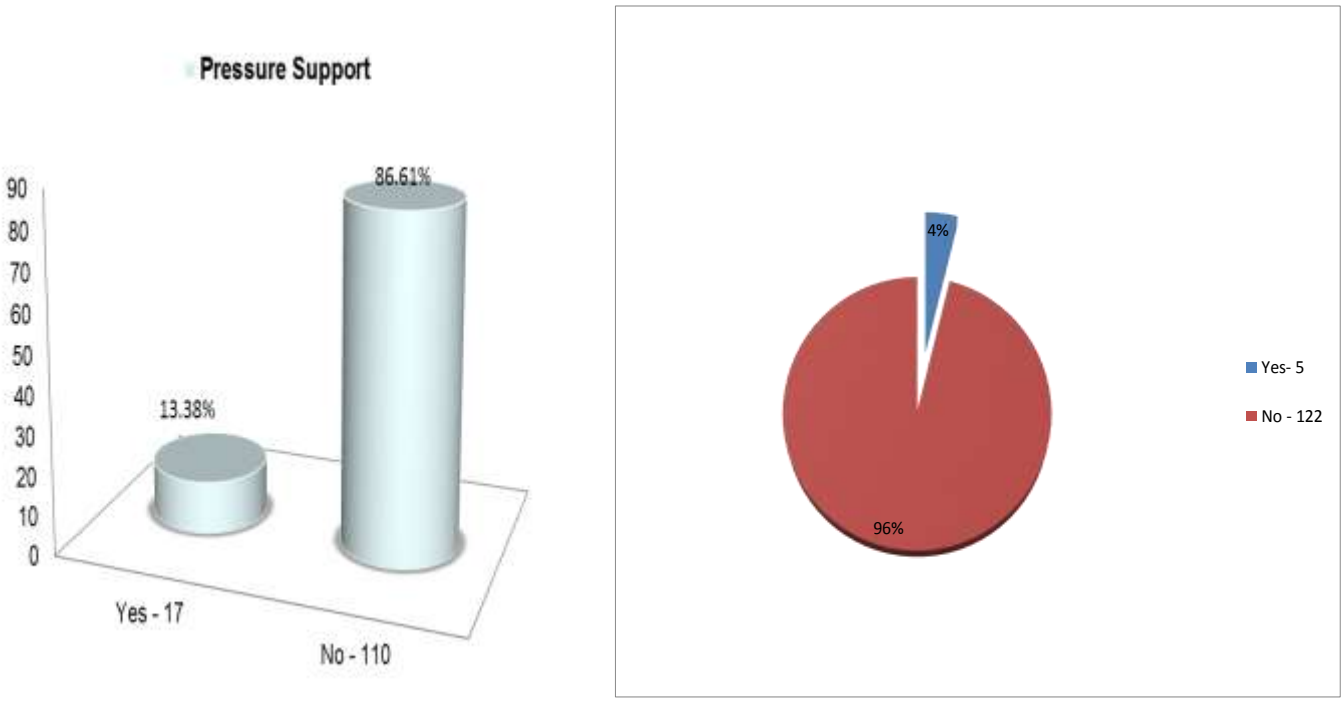
17/127 had blood culture grown for infectious agents, of whom 08 had Klebsiella, 07 had Ecoli, and 01 each had Acinetobacter, Enterococci and Candida .Ascitic culture grew Klebsiella in three and Ecoli in one. Urine had grown Ecoli, Klebsiella and Enterococci in 1 patient each. Sputum grew Klebsiella in two patients.

Fig 6: showing the need for ventilatory support



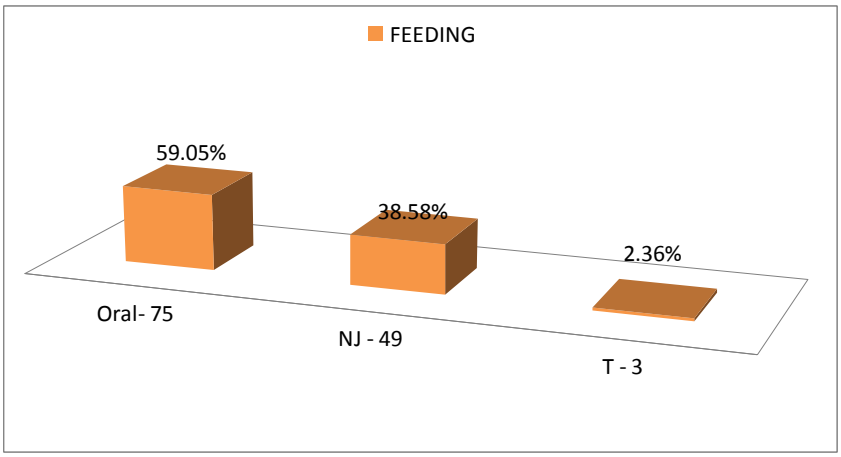
17/127 (13.3%) required ventilatory support, of which 15required invasive ventilatory support.

Fig 7: showing the need for Pressure support and Dialysis support



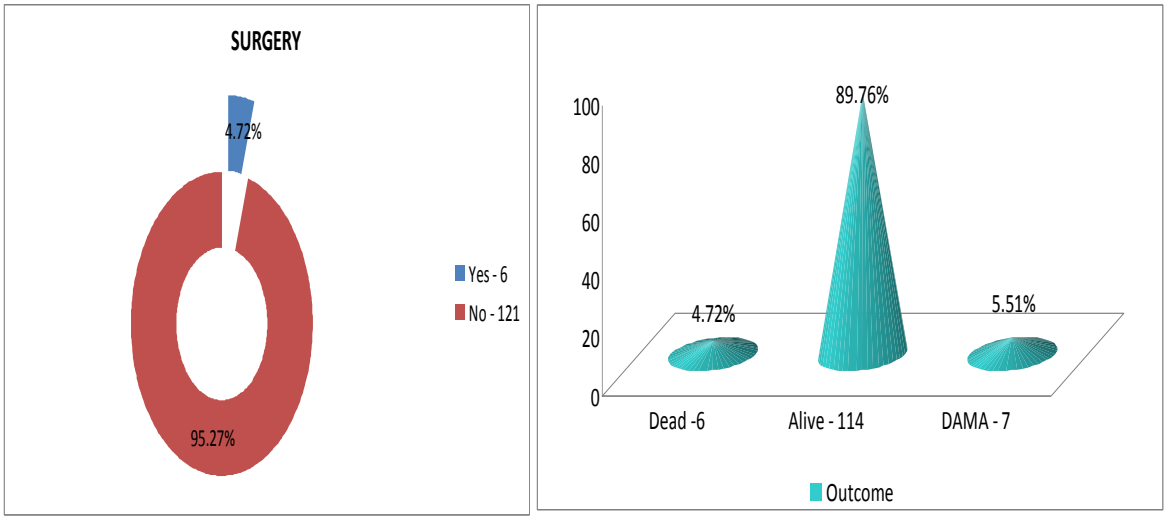
17/127 (13.38%) required pressure support during their hospital stay and about 4% (5/127) required dialysis support.

Fig 8: showing the pattern of mode of nutrition



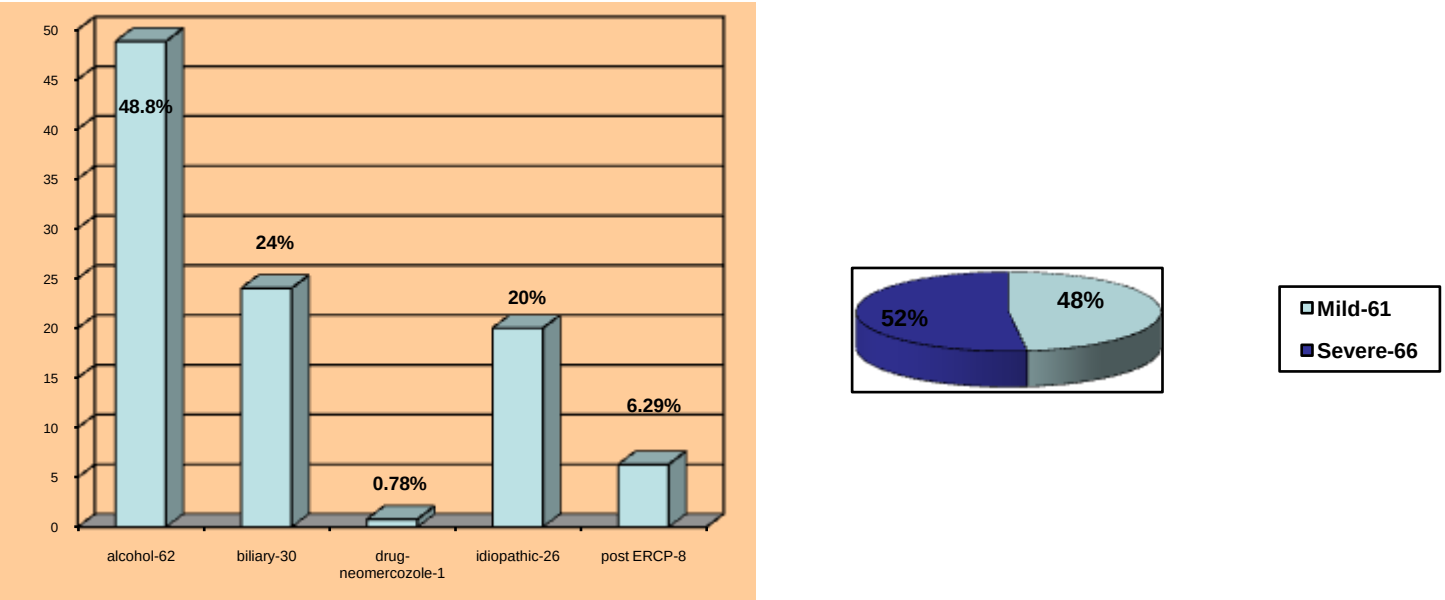
Of all the 127 patients 49 patients (38.58%) required Nasojejunal feeds for their nutrition, 3/127(2.36%) required Total Parenteral Nutrition, and the rest 75/127 (59.05%) was managed by oral feeding.

Fig 9: showing the outcomes in acute pancreatitis (surgery/ alive / dead)



6/127(4.72%) required surgery. Of the 127 patients 114 (89.76%) were alive at the time of discharge , 5.51% (7/127) were discharged agnaist medical advice, and 6/127 (4.72%) died during the hospital stay.

Fig 10:showing aetiological distribution and severity



Alcohol was the most common aetiological factor (48.8% -62/127), second being biliary 24% (30 /127) followed by idiopathic (20%), Post ERCP (6.29%) and finally drugs (1/127) for which Neomercazole was found to be the culprit.

Of all the 127 patients 52% (66/127) had severe disease course where as 48% (61/127) had a mild course.

Table 2: Distribution of first /recurrent episodes of acute pancreatitis

First / recurrent	Mild	Severe	Total
First	51	61	112
Recurrent	11	4	15
Total	62	65	127

Out of the total 127 patients 15/127(11.8%) had recurrent episodes of pancreatitis of which11 were mild and 4 were severe pancreatitis.

Table 3: Aetiology of recurrent acute pancreatitis

Aetiology	Total group	Mild group	Severe group
Idiopathic	7	6	1
Biliary	4	3	1
Alcohol	3	2	1
Post ERCP	1	0	1

Of all the causes of recurrent acute pancreatitis idiopathic group stands first, 7/15 in the total group and 6/11in the mild group. This was followed by biliary, alcohol and post ERCP causes. In the severe group the aetiology behind recurrent acute pancreatitis were shared one each between idiopathic, biliary, alcoholic and post ERCP.

Fig: 11 showing rs 1043618 gene polymorphism

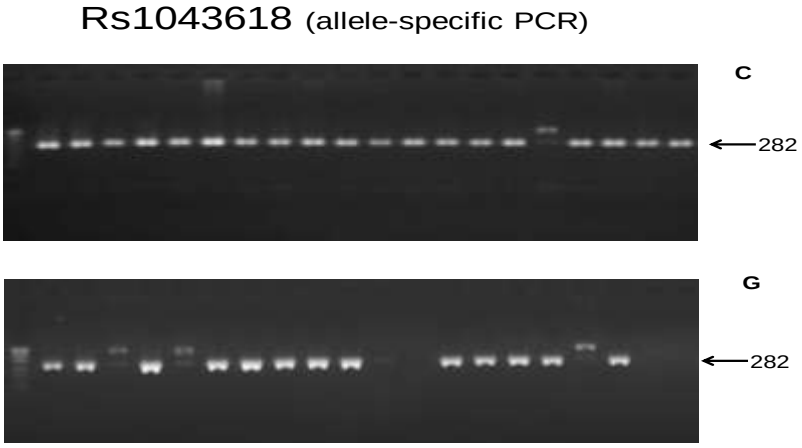


Fig: 12 showing rs 1008438 gene polymorphism

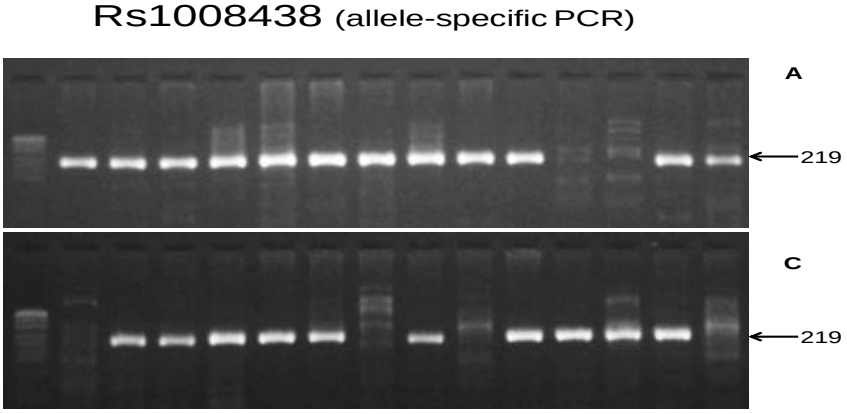


Fig: 13 showing rs 1061581 gene polymorphism

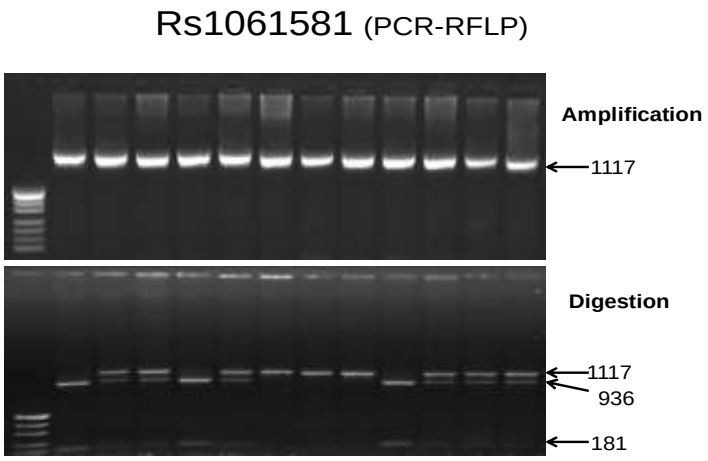
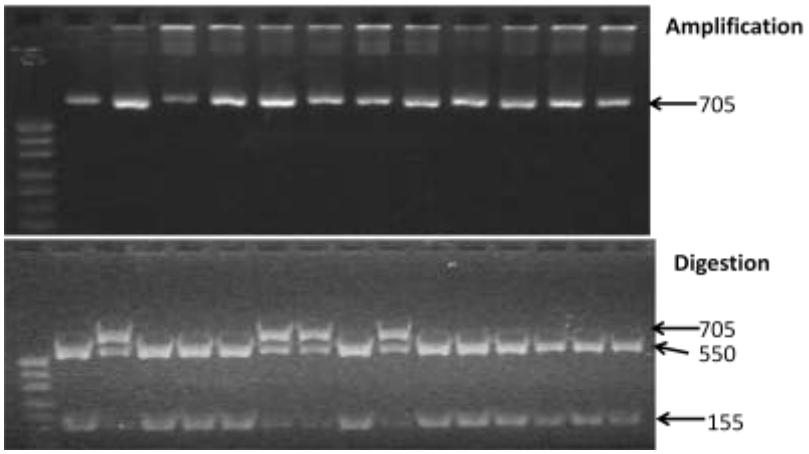


Fig :14 showing rs2227956gene polymorphism



Figures 11 -14 is showing polymorphisms in various SNP namely rs 1043618,

rs 1008438 , rs 1061581 and rs2227956

Table: 4 showing various distribution pattern of rs2227956 gene polymorphism

	Yes /no	CC	CT	TT	P Value
Organ failure	Yes	0	4	25	0.235
	No	1	26	65	
ICU stay	Yes	0	7	33	0.316
	No	1	23	57	
Pulmonary insufficiency	Yes	0	3	23	0.173
	No	1	27	67	
Surgery	Yes	0	0	6	0.337
	No	1	30	84	
Alive	Yes	1	29	78	0.291
	No	0	1	12	
Pressure support	Yes	0	1	16	0.132
	No	1	29	74	
severe	Yes	0	12	52	0.136
	No	1	18	38	

Table 4 showing rs 2227956 gene polymorphism distribution pattern for the variables in acute pancreatitis. Unpooled data analysis did not reveal any statistical significance. Since the numbers of patients in the homozygous CC groups were too small to make any conclusion, we further done a pooled gene analysis (CC/CT vs. TT) for the above variables.

Table : 5 showing various distribution pattern of rs1008438 gene polymorphism

	Yes /no	AA	AC	CC	P Value
Organ failure	Yes	1	20	8	0.425
	No	1	73	18	
ICU stay	Yes	1	28	11	0.443
	No	1	65	15	
Pulmonary insufficiency	Yes	0	18	8	0.345
	No	2	75	18	
Surgery	Yes	0	5	1	0.902
	No	2	88	25	
Alive	Yes	2	82	24	0.738
	No	0	11	2	
Pressure support	Yes	1	13	3	0.320
	No	1	80	23	
severe	Yes	2	47	15	0.328
	No	0	46	11	

Table 5 showing rs1008438 gene polymorphism distribution pattern for the variables in acute pancreatitis. Unpooled data analysis did not reveal any statistical significance. Since the numbers of patients in the homozygous AA groups were too small to make any conclusion, we further done a pooled genetic analysis (AA/AC vs. CC) for the above variables.

Table: 6 showing various distribution pattern of rs1043618 gene polymorphism

	Yes /no	CC	CG	GG	P Value
Organ failure	Yes	8	17	4	0.707
	No	33	47	12	
ICU stay	Yes	14	18	8	0.246
	No	27	46	8	
Pulmonary insufficiency	Yes	6	16	4	0.422
	No	35	48	12	
Surgery	Yes	2	4	0	0.588
	No	39	60	16	
Alive	Yes	35	58	15	0.574
	No	6	6	1	
Pressure support	Yes	6	9	2	0.979
	No	35	55	14	
severe	Yes	23	31	10	0.530
	No	18	33	6	

Table 6 showing rs1043618 gene polymorphism distribution pattern for the variables in acute pancreatitis. Unpooled data analysis did not reveal any statistical significance with any of the above variables.

Table : 7 showing various distribution pattern of rs1061581 gene polymorphism

	Yes /no	AA	AG	GG	P Value
Organ failure	Yes	5	16	8	0.575
	No	22	52	18	
ICU stay	Yes	8	21	11	0.524
	No	19	47	15	
Pulmonary insufficiency	Yes	4	14	8	0.355
	No	23	54	18	
Surgery	Yes	0	5	1	0.316
	No	27	63	25	
Alive	Yes	23	61	24	0.693
	No	4	7	2	
Pressure support	Yes	3	11	3	0.770
	No	24	57	23	
severe	Yes	15	34	15	0.760
	No	12	34	11	

Table 7 showing rs1061581 gene polymorphism distribution pattern for the variables in acute pancreatitis. Unpooled data analysis did not reveal any statistical significance with any of the above variables.

Table: 8 showing various distribution pattern of rs2227956 gene polymorphism

(Pooled data CC/CT genotypes vs TT genotypes)

	Yes /no	CC/CT	TT	P Value
Organ failure	Yes	4	25	0.094
	No	27	65	
ICU stay	Yes	7	33	0.150
	No	24	57	
Pulmonary insufficiency	Yes	3	23	0.063
	No	28	67	
Surgery	Yes	0	6	0.140
	No	31	84	
Alive	Yes	30	78	0.117
	No	1	12	
Pressure support	Yes	1	16	0.044
	No	30	74	
severe	Yes	12	52	0.067
	No	19	38	

Table: 8 showing pooled data distribution pattern of rs2227956 gene polymorphism in patients with the above mentioned variables. Since the numbers of patients who were homozygous CC genotype was too small to make any conclusion, the CC/CT groups were pooled and were compared against homozygous TT group for the further statistical analysis. This pooled data analysis showed significant association between homozygous TT genotype and need for pressure support (P = 0.044). Some of the other variables like overall organ failure, pulmonary insufficiency, and over all severe pancreatitis showed a trend towards association with the correlation with TT genotype.

Table: 9 showing various distribution pattern of rs1008438 gene polymorphism

(Pooled data AA/AC genotypes vs CC genotypes)

	Yes /no	AA/AC	CC	P Value
Organ failure	Yes	21	8	0.359
	No	74	18	
ICU stay	Yes	29	11	0.258
	No	66	15	
Pulmonary insufficiency	Yes	18	8	0.193
	No	77	18	
Surgery	Yes	5	1	0.768
	No	90	25	
Alive	Yes	84	24	0.571
	No	11	2	
Pressure support	Yes	14	3	0.678
	No	81	23	
severe	Yes	49	15	0.580
	No	46	11	

Table: 9 showing pooled data distribution pattern of rs1008438 gene polymorphism in patients with the above mentioned variables. Since the numbers of patients in the homozygous AA groups were too small to make any conclusion, the AA/AC groups were pooled together and were compared against homozygous CC group for the further statistical analysis. This pooled data genetic analysis also did not revealed any statistical correlation.

Table 10: showing correlation between number days in hospital and number of days stayed in ICU against rs1008438 gene polymorphism (pooled data)

Variable	AA/AC Mean +/- SD	CC Mean +/- SD	P Value
Hospital stay in days	11.16±13.993	10.69±16.65	0.886
ICU stay in days	3.42±8.829	2.69±4.831	0.687

The mean number of days stayed in hospital in AA/AC pooled groups and CC genotype groups were 11.16±13.993 and 10.69±16.65 respectively and the corresponding numbers for days stayed in ICU were 3.42±8.829 and 2.69±4.831days respectively. The P value of both these variables did not show any statistical correlation with the rs1008438 gene polymorphisms.

Table 11 : showing correlation between number days in hospital and number of days stayed in ICU against rs1043618 gene polymorphism (pooled data)

Variable	GG/CG Mean +/- SD	CC Mean +/- SD	P Value
Hospital stay in days	11.21±16.425	10.76±10.034	0.871
ICU stay in days	3.44±9.284	2.93±5.255	0.745

The mean number of days stayed in hospital in GG/CG pooled groups and CC genotype groups were 11.21±16.425 and 10.76±10.034 respectively and the corresponding numbers of days stayed in ICU were 3.44±9.284 and 2.93±5.255 days respectively. The P value of both these variables did not show any statistical correlation with the rs1043618 gene polymorphisms.

Table 12 : showing correlation between number days in hospital and number of days stayed in ICU against rs2227956 gene polymorphism (pooled data)

Variable	CC/CT Mean +/- SD	TT Mean +/- SD	P Value
Hospital stay in days	8.16±8.564	12.06±16.00	0.199
ICU stay in days	1.42±3.374	3.90±9.142	0.031

The mean number of days stayed in hospital in CC/CT pooled groups and TT genotype groups were 8.16±8.564 and 12.06±16.00 respectively and the corresponding numbers of days stayed in ICU were 1.42±3.374 and 3.90±9.142 days respectively. The number of days stayed in ICU were found to have a statistically significant association with homozygous TT genotype (P = 0.031). The number of days stayed in hospital did not show any significant correlation with any of the above genotypes.

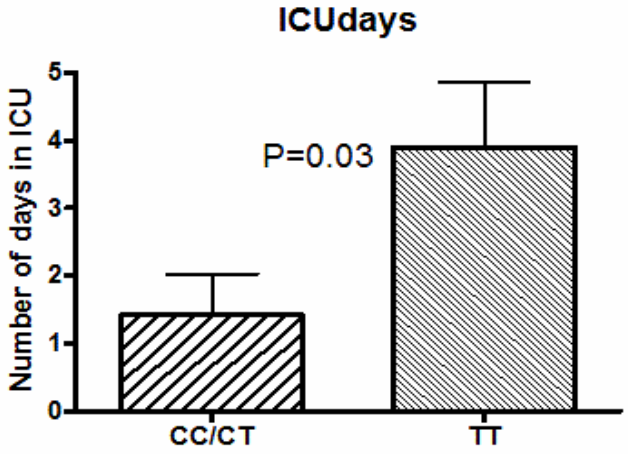


Fig 15 showing number of days spent in ICU in each group (CC/CT and TT genotype group) The bars represent Mean and Standard Error of Mean. The P value was calculated using unpaired t-test with Welch's correction (for non-equal variances).

Table 13: showing correlation between number days in hospital and number of days stayed in ICU against rs1061581 gene polymorphism (pooled data)

Variable	AA/AG Mean ± SD	GG Mean +/- SD	P Value
Hospital stay in days	11.16±13.993	10.69±16.656	0.886
ICU stay in days	3.42±8.829	2.69±4.831	0.687

The mean number of days stayed in hospital in AA/AG pooled groups and GG genotype groups in patients with rs1061581 were 11.16±13.993 and 10.69±16.656 respectively and the

corresponding numbers of days stayed in ICU were 3.42±8.829 and 2.69±4.831 days respectively. The P value of both these variables did not show any statistical correlation with the rs1061581 gene polymorphisms.

DISCUSSION

Acute pancreatitis is defined as a process involving inflammation of pancreas, the surrounding tissues as well as distant organs [(1).] The initial insult of premature activation of enzyme precursors is due to an abrupt increase in the calcium levels in the cytosol[(17)]. This in turn leads to pancreatic parenchymal destruction with activation of coagulation, kinin, complement and fibrinolytic cascades with increased release of cytokines and reactive oxygen metabolites. These results in massive release in the inflammatory cytokines like TNF-α, IL-1, IL-6, IL-8, platelet-activating factor along with reactive oxygen metabolites. The massive inflammatory response resulting from the above changes results in the systemic manifestations of acute pancreatitis. This in turn can leads to increased capillary permeability, hypotension, respiratory and renal failures requiring dialysis and ventillatory supports.

The major heat shock protein for the normal cellular homeostasis in humans is the HSP70. The HSPs has got both the anti-inflammatory as well as the proinflammatory effects, in regulating the human health. These properties of heat shock proteins depends on what is the cell type, the context and the site ,that is whether it is intracellular or extracellular location. The anti-inflammatory effects are ususally intracellular, and is with nuclear factor κB signalling inhibition. The cytokine production is ussually as a result of extracellular effects The other extracellular effects being the induction of regulatory immune cells and reduced inflammation [(27)]. HSP70, although usually is intracellular. But this can be released extracellularly also when the cells are stressed, especially in the setting of necrosis [(28]

Studies have showed that the induction of heat shock proteins (HSPs) are up regulated in acute pancreatitis and also it showed a protective effect in experimental pancreatitis [(29).]

Certain genotypes of HSP70 are associated with higher output of cytokines in response to any inflammatory stimulus.

So Genotype assessments may be important prognostic tools to predict disease severity and the course of acute pancreatitis. Therefore, genotype assessments may also be used to guide treatment or to identify risk populations for severe acute pancreatitis. This study was done to determine whether there is any association between Heat Shock Protein 70 gene polymorphisms and severity of illness and hospital outcomes in patients with acute pancreatitis.

The mean age of patients in our study was around 40 years and there was a male predominance. These can be explained by the fact that, the most common reason found in our study was alcohol (48.8% - 62/127) and in India consumption of alcohol is more common in males than females. This was similar to the findings that were observed in a study conducted in North India by Pooja et al (46).In this study, alcohol was the most common etiological factor (50%) and there was a male predominance.

The mean Simplified Glasgow score was 1.96 ± 1.90 in the total study group, with a value of 0.62 ± 0.68 in the mild group and 3.23 ± 1.80 in the severe group. The raised SGS in the severe group can be explained by the severity of the illness.

Mean PCV observed in the study population (47.37 ± 39.88) was higher than normal, which could be due to inflammatory response and extravasations of fluid into the third space, leading to haemoconcentration. Slightly greater PCV noted in the severe group when compared with the mild group (48.79 ± 38.92 vs. 45.86 ± 41.11) can be explained by greater inflammatory response mounted in the body in cases of severe pancreatitis.

Mean CRP in the severe group was less than that noted in mild group. The peak value of CRP is usually attained between day 3 and 4[(60)]. The above noted variation possibly could be due the difference in the day they presented to our hospital.

The mean amylase and lipase values did not show any correlation with severity of pancreatitis observed. This finding has already been supported in other literatures [(12).]

The number of days in hospital and in the ICU (18.32 ± 20.95 days and 6.26 ± 10.39 days vs. 4.98 ± 2.73days and 0.08 ± 0.45 days) were higher in the severe group when compared with the mild pancreatitis group, which can well be explained with the severity of the disease.

In our study 41.73% had local complications. Acute fluid collection was observed in 37 %(47/127), pseudocyst was observed in 7.08 %(9/127), pancreatic necrosis more than 30 % was observed in 5.51% (7/127) and Pancreatic abscess in 0.7% (1/127). Mifkovic A et al reported similar incidence of acute fluid collections in cases with acute pancreatitis [(61).]The incidence of pseudocyst were noted in about 7.08% in our study. This finding was similar to the finding noted by Baig et al, (8.8%) who conducted a study in eastern India in acute Pancreatitis [(6)]. In our study pancreatic necrosis was found in 5.51%. . Mifkovic A et al, reported incidence of necrosis of pancreas in 15- 25% cases with acute pancreatitis [(61).]The low incidence in our study may be due to the fact that, we have taken only necrosis more than 30 % into account for analysis Pancreatic abscess was observed in 0.7% of total cases. Beger et al in 1998, observed in his study the occurrence of pancreatic abscess in 2-10 % of cases of acute pancreatitis. The less number of pancreatic abscesses in our study could be due to use of

higher generation antibiotics at the onset of infection and earlier surgical intervention in necrotic pancreas [62].

Organ failure was noted in 30/127 (24.04%). Magda A Shaheen et al, in his study also reported similar percentage of acute pancreatitis patients having organ failure [62].In our study population pulmonary insufficiency was the most common organ failure followed by shock, renal failure and Gastrointestinal bleed. Ai-Jun Zhu et al, also observed similar pattern of organ failure in his study, respiratory failure being the most commonest [57].

17/127 had blood culture positive for infectious agents, of whom 08 had Klebsiella, 07 had E Coli, and 01 each had Acinetobacter, Enterococci and Candida. Ascitic culture grew Klebsiella in three and Ecoli in one. Urine had grown Ecoli, Klebsiella and Enterococci in 1 each patients. Sputum grew Klebsiella in two patients. Pramod Kumar Garg et al in 2001, in his study conducted in North India observed Ecoli as the most common organism followed by pseudomonas as cause for sepsis in acute pancreatitis and blood was the most common specimen from which bacteria was isolated .The difference in microbial pattern could well be due to difference in the microbial pattern of infection in different institutions as well as change in protocol of management in the use of antibiotics throughout these years [64].

Of all the 127 patients 49 patients (38.58%) required Nasojejunal feeds and 3/127 (2.36%) required Total Parenteral Nutrition for improving their nutrition during their course of disease.

6/127(4.72%) required surgery during their admission period .In one study from north India ,Babu R Y et al, noted requirement of surgery/ radiological drainage in 80 percentage of

severe pancreatitis on continued follow up [65]. The low percentage in our study could be due to the cross sectional study nature and many of these patients may requires a radiological / surgical intervention in their long term follow up visits.

10.2 % of the toal study patients died during the course of their disease. All the patients who died were having severe pancreatitis .So mortality was observed in 19.6% (13/66) of acute severe pancreatitis . Neoptolemos JP et al and Rau B et al, in two separate studies also observe red 15-30% mortality associated with severe acute pancreatitis [66, 67].

In our study it was observed that 52% (66/127) had severe pancreatitis and rest 48% had mild disease. This was against the general observation of 85% mild disease and 15 % severe disease [1].This can be explained by the fact that our institution being a main tertiary care centre in southern India ,more severe cases were referred from different parts of country to this institution.

Alcohol was the most common aetiological factor (48.8% -62/127), second being biliary 24% (30 /127) followed by idiopathic (20%),Post ERCP (6.29%) and drugs (1/127) for which Neomercazole was found to be the culprit .This was similar to the observation found by Sarfaraz Jalil Baig, et al, from eastern India in which alcohol was the most common aetiology (35.5%) followed by 22.2% due to gallstones, 20% due to trauma, 13.3% due to idiopathic causes, and 8.8% following ERCP [14].

Out of the total 127 patients 15/127(11.8%) had recurrent episodes of pancreatitis of which11 were mild and 4 were severe. This was similar to the observation noted by Peter A Banks et al, in which 10.9% of the study population were found to have recurrent acute Pancreatitis

[68]. Of all the causes of recurrent acute pancreatitis idiopathic group stands first. This was followed by biliary, alcohol and posts ERCP causes. In the severe group the aetiology behind recurrent acute pancreatitis were shared one each between idiopathic , biliary , alcoholic and post ERCP.In one previous study from our institution Sajith K G et al , reported biliary disease (37%) as the most common cause followed by pancreatic divisum (8.5%) and alcohol (6.4%). Multiple aetiologies were seen in 7% of cases, and no cause was found in 32.4% in that study. The difference in the observation can be explained by the large population of recurrent acute pancreatitis (188 Patients)in the previous study when compared with less number of recurrent acute pancreatitis (15 patients) in our present study.

The unpooled genetic data analysis of rs2227956 and rs1008438 gene polymorphism against different outcomes assessed in this study (such as organ failure, need for ICU admission , pulmonary insufficiency ,pressure support ,need for surgery, mortality , and severity of disease) were not showing a significant statistical correlation. Since the numbers of patients in the homozygous CC groups were too small to make any conclusion, we further done a pooled genetic analysis (CC/CT vs. TT and AA/AC vs. CC) for the above variables.

The pooled genetic data analysis of rs 2227956 showed significant correlation between presence of homozygous TT genetic polymorphism and need for pressure support (P = 0.044). Also some of the other variables like overall organ failure, pulmonary insufficiency, and over all severe pancreatitis groups showed a trend towards correlation with presence of homozygous TT gene in rs2227956 genetic polymorphism group. This finding points towards a possibility that those who are having homozygous TT allele with rs2227956 genetic polymorphism are at risk for a severe course disease if they have an episode of acute pancreatitis. The reason why all other parameters did not showed a statistically significant trend could be due to low power of the study because of less number of patients included in this study. Since this study was based on a previous study, which analysed the role of HSP

gene 70 polymorphism in severity of diabetic foot ulcer and outcomes in surgical treatment [40], it might have not helped in calculating an accurate sample size for testing the same polymorphism in acute pancreatitis. The previous study on assessment of the role of HSP gene 70 polymorphism in severity of diabetic foot ulcer and outcomes in surgical treatment was selected as the basis for this present study because that was conducted in the same institution in the same back ground of population so as the genetic makeup of the population will not differ much.

The pooled genetic data distribution of rs1008438 gene polymorphism in patients with the above mentioned variables also did not reveal any statistical correlation.

The unpooled genetic data analysis in patients with rs1061581 and rs 1043618 gene polymorphism to correlate with the same variables mentioned in the above analysis did not reveal any statistical significance.

Further the pooled genetic data of all the four single nucleotide polymorphisms (rs 2227956, rs1008438, rs1061581 and rs 1043618) were analysed to see for any correlation with the number of days hospitalized as well as with the number of days spent in ICU. In the rs 2227956 gene polymorphism group, the mean number of days stayed in hospital in CC/CT pooled groups and TT genotype groups were 8.16±8.564 and 12.06±16.00 respectively and the corresponding numbers of days stayed in ICU were 1.42±3.374 and 3.90±9.142 days respectively. The number of days stayed in ICU were found to be more and was found to have statistically significant in the group with homozygous TT in those with rs 2227956 gene polymorphism (P value = 0.031) than those with CC or CT gene polymorphism. This again correlates with the above observed data.

The pooled genetic data analysis for the other polymorphisms such as rs1008438, rs1061581 and rs 1043618 did not showed any statistically significant correlation with the number of hospital days and days spent in ICU.

Perhaps further studies with a larger population may reveal a statistically significant correlation between rs 2227956 HSP gene 70 polymorphisms and severity of the disease.

SUMMARY
AND
CONCLUSIONS

- Alcohol was the most common cause for acute pancreatitis in this study followed by biliary stones
- Male gender is affected more than females
- Severe Acute Pancreatitis were observed in more than half of the study population
- Local complications were present in 41.73% of study population of which acute fluid collection was the commonest followed by pseudocyst, necrosis and abscess.
- Organ failure was present in one fourth of the study population
- Respiratory insufficiency was the most common organ failure followed by cardiovascular ,renal and gastrointestinal complication
- Klebsiella was the most common organism grown in patient with infection
- The mortality in acute severe pancreatitis was 20 %.
- One tenth of the total population studied had recurrent acute pancreatitis with biliary stones as the most common aetiology after excluding the idiopathic group.
- Homozygous TT rs 2227956 gene polymorphism showed statistically significant correlation with the need for pressure support ,length of ICU stay and it also showed a trend towards significance for overall organ failure, overall severity of the disease and pulmonary insufficiency.
- There is a possibility that those who are having homozygous TT allele with rs2227956 genetic polymorphism are at risk for a severe course of disease if they have an episode of acute pancreatitis.
- Further studies with a larger population may reveal a statistically significant correlation between rs 2227956 HSP gene 70 polymorphisms and severity in acute pancreatitis disease.

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Informed Consent document PATIENT'S INFORMATION

I understand that Dr. UNNIKRISHNAN.L.S. is doing a study to identify the parameters that help in correlating the severity of acute pancreatitis and gene polymorphism. The study involves being interviewed (about the disease) and noting the results of test reports that are being done by the treating doctors for clinical care. A sample of blood will be taken to find out if there is a particular kind of gene pattern that may predispose me (or my patient) to severe illness. The results of the test done in connection with the study may not directly benefit me. They are likely to indirectly benefit other patients with the disease.

I understand that my withdrawal from the study at any time will not affect the treatment being given.

Study Title: Study Number:
Subject's Initials: _____ Subject's Name: _____
Date of Birth / Age:_____ Please initial box
(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]
(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]
(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]
(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]
(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____ Date: _____/_____/_____
Signatory's Name: _____

Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____

Signature of the Witness: _____
Date:_____/_____/_____
Name of the Witness: _____

PROFORMA Study no.

Demographic data

Name :
Age (years) :
Sex : Male / Female
Hosp Num :
Occupation :
Address :

Phone No :

Recruitment data

Outpatient follow-up / Emergency Service / Admitted to ward

Clinical data

Abdominal pain: Duration:
Location: Epigastrium / Generalized / Other
Precipitating factors: Alcohol binge / Fatty food / Trauma / Others / Nil
Vomiting: Yes / No
Breathlessness: Yes / No
Decreased urine output: Yes / No
GI bleed: Yes / No
Fever: Yes / No
Others:
Alcohol consumption: Nil / Social / Alcoholic Qty Type Yrs

Admission characteristics:

Pulse BP Temp Respiratory rate

Simplified Glasgow scoring system (Score >2 in first 48 h = severe)

Variable	Absent	Present
Age >55 yrs		
PaO2 <60 mm Hg		
WBC >15,000/mm^3		
Ca2+ (uncorr.) <8 mg%		
LDH>600 IU/L		
Glucose >180 mg%		
Urea >45 mg%		
Albumin <3.2 g%		
TOTAL SCORE		

CRP :
S. Amylase :
S. Lipase :
PCV :

Chest X Ray: Normal Y / N (if abnormal, at admission or later?)
Effusion Y / N
ARDS Y / N

Ultrasonography:
Gallstones / Biliary dilatation / Pancreatic oedema / Fluid collection / Other

CECT: Done / Not done CTSI (if available:

Findings:

Hospital course:
Admitted during study / Discharged from A&E / Date obtained from records
(now seen in OPD)

I) ***Local complication***: Acute fluid collection
Pseudocyst
Abscess

II) ***Organ Failure***: Yes / No
CVS Systolic BP <90 mm Hg
Respiratory PaO_2 <60 mmHg
Renal Creatinine >2 mg/dl after rehydration
Haematologic GI Bleed >500cc in 24 hours
CNS
Liver

III) ***Sepsis***:

Hospital stay: ____ days DOA DOD

ICU stay: No / Yes If yes, ____ days

Interventions:
Pressor support needed N / Y
Ventilatory support needed N / Y (non-invasive / invasive)
Dialysis support needed N / Y

Feeding: TPN / NJ / Oral
Surgery: Yes / No
Outcome: Dead / Alive

Final Diagnosis: Acute pancreatitis (first attack)
Aetiology :
Severity :

Sl.no	Name	Age	Sex	Hosp:No.	Occupatior	state /country	recruitment
1	Ramjee Ganju	58	Male	876490d	Manual Lal	Jharkand	admitted
2	Bachchi Devi	66	Female	592054d	H wife	Bihar	admitted
3	Dhayalan	54	Male	415357d	Private job	Tamilnadu	admitted
4	Reddyappa	29	Male	887953d	Manual Lal	Andrapradesh	admitted
5	Ramdulalsingh	41	Male	869357d	Private job	Jharkand	admitted
6	Muzaffar	30	Male	896255d	Manual Lal	MP	admitted
7	Topivalli	59	Male	895563d	Teacher	Andrapradesh	admitted
8	Duraiswamy	52	Male	891735	Business	Tamilnadu	admitted
9	Bhuvaneswari	26	Female	637790d	H wife	Tamilnadu	admitted
10	Madhivani	25	Female	266515c	H wife	Tamilnadu	admitted
11	Adhir chandra	43	Male	020376c	Business	assam	admitted
12	Saravanan	30	Male	901120d	Driver	Tamilnadu	admitted
13	Lognathan	48	Male	901250	councillor	Tamilnadu	admitted
14	Thavamani	42	Male	906534d	farmer	Tamilnadu	admitted
15	Muniswamy	33	Male	901446d	Manual Lal	Tamilnadu	admitted
16	kumar	42	Male	099263b	police	Tamilnadu	admitted
17	Rajendran	54	Male	901520d	farmer	Tamilnadu	admitted
18	Vadivel	26	Male	908578d	Manual Lal	Tamilnadu	admitted
19	MarydoraBlah	63	Female	445196b	Teacher	meghalaya	admitted
20	Kumaresan	38	Male	908990d	Manual Lal	Tamilnadu	admitted
21	Melak pradhan	37	Male	917992d	Manual Lal	orissa	admitted
22	Govindaswamy	36	Male	915139d	Manual Lal	Tamilnadu	admitted
23	Anasuyadas	47	Female	917714d	H wife	w Bengal	admitted
24	Nagaraju	37	Male	923104D	Manual Lal	Andrapradesh	admitted
25	Subramani	76	Male	510716B	Manual Lal	Tamilnadu	admitted
26	wrick choudhar	27	Male	932496D	Business	w Bengal	admitted
27	Solomon	30	Male	846266D	Business	Tamilnadu	admitted
28	Gitachanda	41	Female	814079c	H wife	assam	admitted
29	Dasari lakshmi	44	Female	927653d	Business	Andrapradesh	admitted
30	Sahidur Rahma	25	Male	842734d	Business	w Bengal	admitted
31	Kabita karmaka	48	Female	571973c	H wife	w Bengal	admitted
32	Srinivasulu	44	Male	826192d	Manual Lal	Andrapradesh	admitted
33	Balasubramani	23	Male	927872d	student	Tamilnadu	admitted
34	Muniyamma	55	Female	937614d	H wife	Tamilnadu	admitted
35	murukeshan	47	Male	554522b	councillor	Tamilnadu	admitted
36	Asmathunisa	49	Female	937889d	H wife	Tamilnadu	admitted
37	Ravi	23	Male	942471d	Manual Lal	Tamilnadu	admitted
38	krishnareddy	44	Male	942223d	Manual Lal	Andrapradesh	admitted
39	Swarup	22	Male	942694d	student	Tamilnadu	admitted
40	Giridar	44	Male	964647d	Manual Lal	Andrapradesh	admitted
41	parimala	42	Female	962770D	H wife	Tamilnadu	admitted
42	Elumalai	61	Male	968134D	Driver	Tamilnadu	admitted
43	Muskan Sawla	26	Female	982723D	Teacher	UP	admitted
44	Sakunthala	49	Female	284080D	H Wife	Tamilnadu	admitted
45	Anatharaj	28	Male	098786C	Manual Lal	Andrapradesh	admitted
46	Sangeetha	15	Female	845264D	student	Andrapradesh	admitted
47	Pankaj Kumar	35	Male	970753D	Manual Lal	sikkim	admitted
48	Joseph	38	Male	983611D	Manual Lal	Tamilnadu	admitted
49	Ranjith kumar	24	Male	261056D	Manual Lal	Tamilnadu	admitted
50	Mohammed	53	Male	491413D	Manual Lal	Tamilnadu	admitted
51	Mani	57	Male	910038D	clerk	Tamilnadu	admitted
52	Ravindrakuma	32	Male	904013D	Business	Chattisgarh	admitted
53	Manogaran	31	Male	992588D	Engineer	Tamilnadu	admitted
54	Govindaraj	30	Male	992935D	Business	Tamilnadu	admitted
55	Rangaraj	36	Male	995347d	Business	Tamilnadu	admitted

56	Thullasamma	25	Female	002237f	H Wife	Andrapradesh	admitted
57	Srinivasan	36	Male	005245f	shop keepe	Andrapradesh	admitted
58	Dhachinamurth	45	Male	008123f	farmer	Tamilnadu	admitted
59	Yania Haji	60	Female	003936f	H Wife	arunachal Pra	admitted
60	Raja	39	Male	046151f	farmer	Tamilnadu	admitted
61	Rajesh	27	Male	111409D	student	Andrapradesh	admitted
62	Munisamy	35	Male	032267f	Manual Lal	Tamilnadu	admitted
63	Irudayamary	60	Female	061510f	H Wife	Tamilnadu	admitted
64	Prasad	35	Male	068700f	Manual Lal	Andrapradesh	admitted
65	Sam	30	Male	750089d	Business	Tamilnadu	admitted
66	kothandan	51	Male	069561f	Manual Lal	Tamilnadu	admitted
67	Dileepkrishna	29	Male	071884f	Manual Lal	Andrapradesh	admitted
68	Debabradadas	48	Male	331039b	Business	w Bengal	admitted
69	Meeta roy chou	46	Female	823463d	H Wife	Jharkand	admitted
70	kumaravel	49	Male	950439b	Manual Lal	Tamilnadu	admitted
71	Sathishkumar	35	Male	998876b	student	Tamilnadu	admitted
72	Sounderajan	47	Male	077436f	Manual Lal	Tamilnadu	admitted
73	Joyceevasanth	50	Female	642516b	H Wife	Tamilnadu	admitted
74	Jeyadurga	15	Female	089408f	student	Tamilnadu	admitted
75	venkatesan	31	Male	089833f	shop keepe	Tamilnadu	admitted
76	Asparabarua	58	Female	076149f	H Wife	bangladesh	admitted
77	Murugesan	50	Male	944145f	Manual Lal	Tamilnadu	admitted
78	Ramanaiah	58	Male	098588f	Manual Lal	Tamilnadu	admitted
79	Bhavani	22	Female	910912d	H Wife	Tamilnadu	admitted
80	Sarguna	55	Female	098281f	H Wife	Tamilnadu	admitted
81	Goaspeer	27	Male	094919f	Manual Lal	Andrapradesh	admitted
82	Sivappa	41	Male	110120f	Manual Lal	Andrapradesh	admitted
83	Ataullah khan	27	Male	113971f	Manual Lal	Andrapradesh	admitted
84	Karthikeyan	34	Male	107220f	Manual Lal	Tamilnadu	admitted
85	Murthi	39	Male	098623f	Manual Lal	Tamilnadu	admitted
86	Muniratnamred	64	Male	116317f	Manual Lal	Andrapradesh	admitted
87	Malliga	56	Female	112687f	H Wife	Tamilnadu	admitted
88	Parvathi amma	70	Female	350047c	H Wife	Tamilnadu	admitted
89	Jalapati	37	Male	058754f	Business	Tamilnadu	admitted
90	Ekambram	63	Male	373384a	Manual Lal	Tamilnadu	admitted
91	Jayaganesh	22	Male	473681c	Manual Lal	Tamilnadu	admitted
92	Manoharan	39	Male	094808b	Manual Lal	Tamilnadu	admitted
93	Jithinroy	21	Male	124338f	student	kerala	admitted
94	Partheeban	32	Male	993654b	Manual Lal	Tamilnadu	admitted
95	Sudhakar	28	Male	937536d	Business	Tamilnadu	admitted
96	Kavadiguravaia	33	Male	139079f	Manual Lal	Andrapradesh	admitted
97	Manimaran	43	Male	133396f	Manual Lal	Tamilnadu	admitted
98	Mahalingam	34	Male	914781d	Manual Lal	Tamilnadu	admitted
99	Janakiramanaia	30	Male	136131f	Manual Lal	Andrapradesh	admitted
100	Firoza khation	47	Female	145536f	H Wife	Jharkand	admitted
101	Rajendran	57	Male	430958d	Manual Lal	Tamilnadu	emergency
102	Dilipkumar	31	Male	147134f	Business	w Bengal	admitted
103	Vijaya	40	Female	139364f	H Wife	Tamilnadu	admitted
104	Mahesh	29	Male	133518f	Business	Andrapradesh	admitted
105	Ekambaram	30	Male	130489f	Business	Tamilnadu	admitted
106	Poongodi	34	Female	130348c	H Wife	Tamilnadu	admitted
107	Bashirudden	62	Male	159572f	Business	Tamilnadu	admitted
108	Sriramlu	50	Male	162220f	Manual Lal	Andrapradesh	admitted
109	Agayakumar	38	Male	169127f	Manual Lal	Bihar	admitted
110	Babu	31	Male	171708f	Manual Lal	Tamilnadu	admitted
111	Gopi	34	Male	174326f	security gu	Tamilnadu	admitted

112	Sreedevi	34	Female	139347f	H Wife	Tamilnadu	admitted
113	Gousiya	18	Female	119454f	student	Andrapradesh	admitted
114	Muniswamy	28	Male	174438f	Manual Lal	Andrapradesh	admitted
115	Mahalakshmi	43	Female	001903B	ANM CMC	Tamilnadu	admitted
116	Devit	29	Male	192884f	Manual Lal	Tamilnadu	admitted
117	Venkateshbabu	37	Male	889196d	Driver	Tamilnadu	admitted
118	Suryakala	46	Female	849024a	H Wife	Tamilnadu	admitted
119	Das	46	Male	198858f	Driver	Tamilnadu	emergency
120	Indeshwarihish	68	Male	218842f	shop keepe	karnataka	admitted
121	Venkatesan	25	Male	222737f	Driver	Tamilnadu	admitted
122	Rossiah	69	Male	222410F	no job	Andrapradesh	admitted
123	Juyashankar	27	Male	620152d	Driver	Andrapradesh	admitted
124	Natraagaruvel	26	Female	543533d	Business	Chattisgarh	admitted
125	Poongodi	35	Female	236987f	H Wife	Tamilnadu	admitted
126	Ramakrishna r	42	Male	234980f	no job	Andrapradesh	admitted
127	Venkateshbba	55	Male	234948f	no job	Andrapradesh	admitted

male	93
female	34

73.228	0	0	0	0
26.772	0	0	0	0
73.22				
26.77				

p.complaint	ppt: factors	SGSscore	CRP	amylase	lipase	PCV
pain, vomiting, fever	Nil	3	154	370	296	350
pain, vomiting, fever	post ERCP	2	>218	829	1957	38
pain,vomiting,dyspnoea,fever	alcohol	4	>218	287	545	35
pain ,vomiting	alcohol,hypertriglyceridemia	1	>218	157	396	38
pain, vomiting, dyspnoea	Nil	4	>216	509	209	32
pain ,vomiting	alcohol	2	77	500	861	38
pain	Nil	2	171	3922	7340	40
pain	post ERCP	2	100	2077	3608	21
pain ,vomiting	Nil	0	11.2	1485	3502	39
pain, vomiting, dyspnoea	Nil	3	218	1678	3370	61
pain,vomiting,dyspnoea,fever	Nil	6	218	50	71	18
pain,vomiting,dyspneoa,fever,↓ urine	alcohol	4	218	276	261	44
pain, vomiting, dyspnoea	alcohol	1	218	1104	2418	35
pain, vomiting, fever	Nil	0	15	261	836	29
pain ,vomiting	alcohol	1	218	894	3112	45
pain ,vomiting	alcohol	3	25	512	3014	57
pain ,vomiting	alcohol	2	196	129	185	37
pain ,vomiting	alcohol	1	218	128	246	42
pain,vomiting,dyspnoea,fever	post ERCP	3	214	616	1049	37
pain,vomiting,dyspnoea,fever	alcohol	5	218	1004	1228	31
pain ,vomiting	Nil	1	20.2	290	247	47
pain ,vomiting	alcohol	2	30.6	351	540	42
pain ,vomiting	post ERCP	1	75	1825	5081	34
pain,vomiting,dyspneoa,fever,↓ urine	alcohol	6	197	142	383	52
pain ,vomiting	Nil	6	200	3219	18250	42
pain ,vomiting	alcohol	4	197	509	271	36
pain ,vomiting	alcohol	0	148	1375	2756	38
pain,vomiting,dyspnoea,fever	post ERCP	1	10	679	1528	37
pain,vomiting,dyspneoa,fever,↓ urine	Nil	6	218	3278	3032	50
pain ,vomiting	post ERCP	0	79	486	696	42
pain ,vomiting	Nil	1	6	4134	14280	38
pain ,vomiting	Nil	0	47	1876	5258	37
pain ,vomiting	Nil	3	197	23	443	44
pain, vomiting, dyspnoea	Nil	2	185	1810	2330	27
pain,vomiting,dyspnoea,fever	alcohol	1	116	479	1311	45
pain, vomiting, fever	Nil	1	157	953	1783	36
pain,vomiting,dyspnoea,fever	alcohol	3	197	151	255	40
pain,vomiting,dyspnoea,fever	alcohol	5	197	900	526	40
pain ,vomiting	Nil	0	77	2639	7248	42
pain ,vomiting	alcohol	1	82	261	815	39
pain,vomiting,dyspnoea,fever	Nil	4	197	167	693	36
Pain	alcohol	4	197	263	771	47
pain	Nil	0	48	1234	1549	42
pain ,vomiting	Nil	1	10.8	225	418	31
pain ,vomiting	alcohol	0	85	288	587	45
pain ,vomiting	Nil	0	2.97	889	2368	360
pain ,vomiting	nil	0	7.2	80, 215	67	41
pain ,vomiting	Nil	1	37.5	180	564	45
pain	Nil	0	163	1034	3796	45
pain,vomiting,dyspnoea,fever	Nil	2	178	4490	9362	46
pain ,vomiting	Nil	1	57.2	1227	1598	40
pain,vomiting,dyspnoea,fever	Nil	4	40	1513	2487	46
pain ,vomiting	alcohol	4	133	1260	1608	62
pain, vomiting, fever	alcohol	3	173	530	626	60
pain ,vomiting	alcohol	2	129	382	462	36

pain, vomiting, fever	Nil	5	189	3000	2815	30	
pain,vomiting,dyspnoea,fever	alcohol	5	153	296	1520	61	
pain,vomiting,dyspnoea,fever	alcohol	5	80	1897	1616	52	
pain, Fever	Nil	4	88.2	962	2161	43	
pain ,vomiting	alcohol	2	190	863	2006	53	
pain ,vomiting	Nil	2	21.4	960	1580	48	
pain ,vomiting	alcohol	6	184	1204	2061	60	
pain, vomiting, dyspnoea	Nil	6	190	1594	4314	44	
pain ,vomiting	alcohol	0	49	1034	910	43	
pain, vomiting, fever	alcohol	2	186	152	163	44	
pain ,vomiting	Nil	0	37.9	1034	864	43	
pain, vomiting, dyspnoea	alcohol	1	111	85	92	44	
pain ,vomiting	alcohol	0	37.9	1712	5204	46	
pain ,vomiting	fatty food	1	95.1	297	780	27	
pain ,vomiting	fatty food	1	130	484	1488	42	
pain ,vomiting	Nil	0	7190	50.192	332.88	-	
pain ,vomiting	alcohol	0	91.2	930	2064	45	
pain ,vomiting	Nil	1	52	603	3050	38	
pain ,vomiting	Nil	0	846	2698	4200	32	
pain, vomiting, dyspnoea	alcohol	1	122	572	1776	42	
pain, vomiting, dyspnoea	Nil	4	170	203	279	37	
pain ,vomiting	fatty food	2	107	3303	6678	57	
pain ,vomiting	alcohol	3	120	414	814	42	
pain ,vomiting	fatty food	0	36.8	2029	2914	40	
pain ,vomiting	Nil	1	132	1162	1944	46	
pain ,vomiting	alcohol	0	190	711	1373	40	
pain, vomiting, dyspnoea	alcohol	3	136	1110	3494	42	
pain ,vomiting	Nil	1	190	1104	1601	43	
pain ,vomiting	alcohol	0	46	198	234	40	
pain ,vomiting	alcohol	0	190	241	381	48	
pain, vomiting, dyspnoea	Nil	6	190	999	864	52	
pain ,vomiting	fatty food	0	190	2464	949	42	
pain ,vomiting	Nil	5	190	1651	2954	48	
pain ,vomiting	Nil	0	34.7	2663	2950	54	
pain ,vomiting	alcohol	1	21.6	3419	6550	48	
pain, vomiting, dyspnoea	alcohol	4	42	494	567	48	
pain ,vomiting	Nil	1	116	144	170	42	
pain ,vomiting	Nil	0	129	427	668	44	
pain, vomiting, dyspnoea	alcohol	5	190	1167	1394	48	
pain ,vomiting	alcohol	1	112	967	1118	40	
pain ,vomiting	alcohol	4	150	398	776	48	
pain ,vomiting	alcohol	0	152	368	346	41	
pain ,vomiting	alcohol	1	11	226	331	45	
pain ,vomiting	alcohol	4	190	1453	2018	44	
pain ,vomiting	fatty food	1	21.4	92	252	42	
pain ,vomiting	alcohol	1	53.2	243	549	48	
pain,vomiting,dyspnoea,fever	alcohol	5	106	236	843	48	
pain, vomiting, dyspnoea	Nil	1	190	1766	3667	46	
pain ,vomiting	alcohol	1	140	550	272	53	
pain ,vomiting	alcohol	0	61	1017	1172	42	
pain ,vomiting	alcohol	1	59	426	439	29	
pain ,vomiting	Nil	2	31	927	937	42	
pain ,vomiting	alcohol	1	95.1	583	392	45	
pain ,vomiting	alcohol	1	42	429	651	30	
pain ,vomiting	alcohol	1	101	637	1321	60	
pain, vomiting, dyspnoea	alcohol	4	140	582	1620	45	

pain ,vomiting	Nil	0	114	255	1314	38
pain ,vomiting	Nil	1	100	445	1267	48
pain, vomiting, dyspnoea	alcohol	5	190	587	996	54
Pain	Nil	0	78.5	211	605	33
pain,vomiting,dyspnoea,fever	Nil	2	184	336	691	41
pain	Nil	0	163	496	1150	53
pain	Nil	0	79.2	887	2512	30
pain, vomiting, dyspnoea	Nil	0	9.44	237	227	38
pain	Nil	2	12.6	1050	1090	39
pain, vomiting, dyspnoea	alcohol	3	190	478	1974	62
pain, vomiting, dyspnoea	Nil	3	127	322	587	40
pain ,vomiting	alcohol	0	102	675	3071	45
pain ,vomiting	Nil	0	80	4522	5197	40
pain ,vomiting	Nil	0	100	239	400	40
pain ,vomiting	Nil	4	122	239	237	34
pain ,vomiting	alcohol	0	95.3	153	244	40

0
0

CHEST XRAY	USG	CT
left sided effusion	not done	bulkypancreas,pseudocyst
bilateral Effusion	normal	bulkypancreas,necrosis>30%,ascites
bilateral Effusion	Pancreaticedema	bulkypancreas , collections,splenic vein thrombosis
Normal	normal	bulky pancreas necrosishead <30%
bilateral Effusion	collections	bulky pancreas,collections,pseudocyst
left sided effusion	Pancreaticedema,collections	pancreatic edema collections , necrosis >30%
Normal	cholelithiasis	not done
Normal	pancreatic edema	not done
Normal	gallstones ,pancreatic edema	not done
bilateral Effusion	pancreatic edema ,fluidcollect	pancreatic edema collections
left sided effusion	normal	pancreaticedema,fluid collections
left sided effusion	normal	ascites,pancreatic edema
bilateral Effusion	pancreatic edema	Pancreatic edema,fluid collection
Normal	cholelithiasis	not done
Normal	pancreaticedema	not done
left sided effusion	pan edema ,collections	not done
bilateral Effusion	normal	gall stones, pan edema collections
left sided effusion	pan edema	not done
bilateral Effusion	pancretic edema,collections	panedema,collection,bilateral pleu effusion
left sided effusion	panedema,collections	>30%necrosis,collections
Normal	pancreatic edema,collection	pseudocyst
Normal	pan edema	not done
Normal	normal	not done
Normal	fluid collection	fluid collection
bilateraleffusion, ARDS	not done	bulkypan,nec <30%,CTSI=6
bilateral Effusion	not done	bulky pancreas ,ascites
Normal	pacreatic edema	not done
Normal	normal	not done
bilateral Effusion	pancr edema ,collection	bulky pancreas,collections,
Normal	normal	not done
Normal	gallstones ,pancreatic edema	not done
Normal	gallstones	not done
Normal	pancreati edema,Gb sludge	not done
bilateral Effusion	pan edema,gall stone, collecti	cholelithiasi,pan edema,collection, ascites
left sided effusion	cholelithiasis	not done
Normal	pancredema	not done
left sided effusion	pancr edema ,collection	pan edema ,collection
left sided effusion	pancredema,collection	pan edema,necrosis>30%,collection
Normal	biliary dilatation,panedema	not done
Normal	normal	not done
Normal	not done	pancreatic edema
bilateral effusion	bulky pancreas	bulky pancreas, splenic vein thrombosis
Normal	pancreatic edema	not done
Normal	pancreatic edema	not done
Normal	pancreatic edema	not done
Normal	pan edema	not done
Normal	fluid collection	pseudocyst,necrosis<30%, splenic vein thrombosis
Normal	not done	not done
Normal	pancreatic edema	not done
bilateraleffusion, ARDS	gallstones	not done
Normal	pancreatic edema	pancreatic edema
Normal	pancreatic edema	pancreatic edema,fluid collection, gross ascites,
Normal	pancreatic edema	necrosis >30 %, pancreatic edema, fluid collection
Normal	not done	pancreatic edema, fluid collection
left sided effusion	pancreatic edema fluid collect	pancreatic edema, fluid collection,necrosis<30%

bilateral Effusion	fluid collection	fluid collection, necrosis >30 %, gross ascites
left sided effusion	normal	pancreatic edema, fluid collection,splenic vein thromb
bilateral Effusion	pancreatic edema	pancreatic edema, fluid collection,splenic vein thromb
left sided effusion	pancreatic edema	pancreatic edema
bilateral Effusion	pancreatic edema	pancreatic edema, fluid collection, necrosis<30% ,grc
left sided effusion	pancreatic edema, fluid collec	biliary dilatation, gross ascites
bilateral Effusion	gall stone	gall stone
bilateral Effusion	pancreatic edema	pancreatic edema, fluid collection, necrosis <30 %
Normal	Gifally fever	pan odena
bilateral Effusion	not done	pancreatic edema
Normal	pancreatic edema	not done
bilateral Effusion	panedema,collections, GB slu	not done
Normal	pancreatic edema	not done
Normal	bilateral	pancreatic edema
Normal	not done	pancreatic edema
Normal	pancreatic edema	pancreatic edema
left sided effusion	normal	pancreatic edema, fluid collection, necrosis <30 %
Normal	biliary dilatation	biliary dilatation
Normal	bulky pancreas	not done
left sided effusion	normal	pan edema,nec<30%,plenic vein thrombosis,
Normal	pancreatic edema	pancreatic edema,
Normal	pancreatic edema	not done
Normal	normal	fluid collection
Normal	gallstones Biliary dil	not done
Normal	bulky pancreasGall stones	not done
Normal	bulky pancreas	not done
left sided effusion	not done	pancreatic edema,splenic vein thrombosis
Normal	bulky pancreas	not done
Normal	bulky pancreas	not done
Normal	bulky pancreas	not done
left sided effusion	pancreatic edema ,fluid colle	pancreatic edema,fluid collection, gross ascites
Normal	normal	not done
left sided effusion	biliary dilatation	pancreatic edema, fluid collection, splenic vein throm
Normal	gall stones	gall stone
Normal	normal	not done
bilateral Effusion	pancreatic edema ,fluid colle	pancreatic edema, fluid collection,pseudocyst
Normal	cholelithiasis,biliary dilatation	gall stone,biliary dilatation
Normal	not done	pancreatic edema
bilateral Effusion	pancreatic edema	pan edema ,collection,ascites
Normal	panereatic edema	not done
left sided effusion	not done	pancreatic edema, fluid collection
Normal	panereatic edema	not done
Normal	normal	not done
bilateral Effusion	not done	pancreatic edema, fluid collection,necrosi>30%
Normal	pancreatic edema	pancreatic edema
Normal	pancreatic edema	not done
bilateral Effusion	pancreatic edema	pancreatic edema, fluid collection,ascites
bilateral Effusion	not done	pancreatic edema,fluid collection, gross ascites, splei
Normal	not done	pancreatic edema, fluid collection
Normal	biliary dilatation	not done
Normal	gall stones,biliary dilatation	not done
Normal	normal	not done
Normal	normal	not done
Normal	normal	pancreatic edema
bilateral Effusion	normal	pancreatic edema, necrosis >30 %
left sided effusion	not done	pancreatic edema, necrosis<30 %

Normal	biliary dilatation,pancreatic ed	not done
bilateral Effusion	gallstones,pancreatic edema,	gallstones,pancreatic edema, psudocyst
bilateral Effusion	pancreatic edema, fluid collec	not done
Normal	gallstones	not done
left sided effusion	nil	pancreatic edema, necrosis<30 %
Normal	gallstones	not done
Normal	other	paner-edema
Normal	pancreatic oedema	not done
Normal	other	paner-edema
Normal	pancreatic oedema	pancreatic oedema, collection-peripancreata, splence
Normal	pancreatic oedema, fluid colle	not done
Normal	pancreatic oedema, fluid colle	not done
Normal	other	paner-edema
Normal	normal	paner-edema
Normal	pancreatic oedema, fluid colle	pan edemo, resipanereelu collectear
Normal	pancreatic oedema	not done

local comp	org failure	sepsis	bacteremia	H:stay	icu adm	icu days	pr supp	vent:spp
pseudocyst	no	no	no	17	no	0	no	no
acute fluid collection	no	no	no	11	yes	5	no	no
acute fluid collection	resp,renal	no	no	17	yes	3	no	no
no	no	no	no	3	no	0	no	no
acute fluid collection, ps	resp	no	ecoli,pan drain	89	yes	20	no	yes,invasive
acute fluid collection	no	no	no	13	no	0	no	no
no	no	no	no	3	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	3	no	0	no	no
acute fluid collection	resp	no	no	13	no	0	no	no
acute fluid collection	resp,renal,(	yes	NFGNB-Blood	12	yes	12	yes	yes,invasive
acute fluid collection	resp,renal,(	no	no	16	yes	3	yes	yes,invasive
acute fluid collection	no	no	no	8	yes	3	no	no
no	no	no	no	7	no	0	no	no
no	no	no	no	6	no	0	no	no
acute fluid collection	no	no	no	5	yes	2	no	no
acute fluid collection	no	yes	NFGNBBlood	6	yes	2	no	no
no	no	no	no	4	no	0	no	no
acute fluid collection,ab	cvs	yes	urine-ecoli	42	yes	10	yes	no
acute fluid collection	resp	no	no	17	yes	1	no	no
pseudocyst	no	no	no	8	no	0	no	no
no	no	no	no	2	no	0	no	no
no	no	no	no	7	no	0	no	no
acute fluid collection	cvs, resp	yes	candida-Blood	37	yes	15	yes	yes,invasive
no	cvs, resp	yes	blod -Ecoli	4	yes	4	yes	yes,invasive
acute fluid collection	resp	no	no	7	yes	4	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	9	no	0	no	no
acute fluid collection	resp,renal,	yes	blood -klebsiell	89	yes	30	yes	yes,invasive
no	no	no	no	8	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	7	no	0	no	no
acute fluid collection	no	yes	ascites-klebsiel	9	yes	3	no	no
no	no	no	no	8	yes	3	no	no
no	no	no	no	4	yes	2	no	no
acute fluid collection, ps	no	yes	blood -enteroco	8	yes	4	no	no
acute fluid collection	resp	yes	blood,ascites-E	20	yes	7	no	yes,invasive
no	no	no	no	6	no	0	no	no
no	no	no	no	4	no	0	no	no
no	no	no	no	3	no	0	no	no
no	cvs, resp	no	no	2	no	0	yes	no
no	no	no	no	3	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	4	no	0	no	no
no	no	no	no	3	no	0	no	no
pseudocyst	no	no	no	4	no	0	no	no
no	no	no	no	3	no	0	no	no
no	no	no	no	4	no	0	no	no
no	cvs, resp	yes	no	61	yes	61	yes	yes,invasive
no	no	no	no	4	no	0	no	no
acute fluid collection, ps	cvs, resp, (	yes	Ascites-klebsie	22	yes	13	yes	no
acute fluid collection	no	no	no	30	yes	15	no	no
acute fluid collection	no	no	Ascites-klebsie	16	no	0	no	no
acute fluid collection	no	no	no	7	no	0	no	no

acute fluid collection	no	no	urine-klebsiella	20	yes	5	no	no
acute fluid collection	resp	no	no	16	yes	10	no	yes,invasive
acute fluid collection	no	yes	blood-ecoli	34	yes	10	no	no
no	cvs	no	no	7	yes	3	yes	no
acute fluid collection	no	no	no	10	no	0	no	no
acute fluid collection	no	no	no	18	yes	3	no	no
acute fluid collection	resp,renal,(	yes	yes	58	yes	40	yes	yes,invasive
acute fluid collection	no	no	no	11	yes	3	no	no
no	no	no	no	6	no	0	no	no
no	no	no	no	4	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	3	no	0	no	no
no	no	no	no	8	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	5	no	0	no	no
acute fluid collection	no	no	no	6	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	3	no	0	no	no
no	no	no	urine enterococ	16	no	0	no	no
acute fluid collection		yes	blood cultureNI	24	yes	5	no	no
no	no	no	no	6	no	0	no	no
no	no	yes	blood ecoli	10	no	0	no	no
no	no	no	no	8	no	0	no	no
no	no	no	no	7	no	0	no	no
no	no	no	no	7	no	0	no	no
no	cvs, resp,r	no	no	3	no	0	yes	yes,invasive
no	no	no	no	2	no	0	no	no
no	no	no	no	4	no	0	no	no
no	no	no	no	2	no	0	no	no
acute fluid collection	no	no	no	11	no	0	no	no
no	no	no	no	6	no	0	no	no
acute fluid collection	no	no	no	11	no	0	no	no
no	no	no	bloodecoli	4	no	0	no	no
no	no	no	no	2	no	0	no	no
acute fluid collection, ps	no	no	no	6	no	0	no	no
no	no	no	blood ecoli	11	no	0	no	no
no	no	no	no	3	no	0	no	no
acute fluid collection	cvs, resp,r	yes	blood klebsiella	43	yes	18	yes	yes,invasive
no	no	no	no	1	no	0	no	no
acute fluid collection	no	yes	blood staph	11	no	0	no	no
no	no	no	no	5	no	0	no	no
no	no	no	no	6	no	0	no	no
acute fluid collection	resp	yes	blood ecoli	2	yes	2	no	yes,invasive
no	no	no	no	0	no	0	no	no
no	no	no	no	1	no	0	no	no
acute fluid collection	resp	yes	blood-kleb,acin	16	yes	8	no	noninvasive
acute fluid collection	resp	no	no	18	yes	18	no	no
acute fluid collection	no	no	no	4	no	0	no	no
no	no	no	no	7	no	0	no	no
no	no	no	no	4	no	0	no	no
no	no	no	no	3	no	0	no	no
no	no	no	no	2	no	0	no	no
no	no	no	no	3	no	0	no	no
acute fluid collection	no	no	no	8	no	0	no	no
no	resp	yes	spu-ecoli,kleb,I	11	yes	2	no	no

no	no	no	no	9	no	0	no	no
pseudocyst	no	no	no	7	yes	2	no	no
acute fluid collection	cvs, resp,r	yes	blood-kleb,/spu	15	yes	15	yes	no
no	no	no	no	10	no	0	no	no
pseudocyst	resp,cvs	yes	yes	35	yes	14	yes	yes,invasive
no	no	no	no	4	no	0	no	no
no	no	no	no	8	no	0	no	no
no	no	no	no	1	no	0	no	no
no	no	no	no	14	no	0	no	no
acute fluid collection	resp	no	no	14	yes	5	no	no
acute fluid collection	cvs,resp	no	no	105	yes	15	yes	yes,invasive
acute fluid collection	no	no	no	5	no	0	no	no
no	no	no	no	4	no	0	no	no
no	no	no	no	10	no	0	no	no
acute fluid collection	cvs	no	no	19	no	12	yes	noninvasive
acute fluid collection	no	no	no	3	no	0	no	no

dialysis	feeding	surgery	out come	first/recu	aetiology	severity
no	NJ	no	alive	first	idiopathic	severe
no	oral	no	alive	first	post ERCP	severe
no	NJ	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol,hypertriglyceridemia	mild
no	NJ	yes	alive	first	idiopathic	severe
no	NJ	yes	alive	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	post ERCP	mild
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	idiopathic	severe
yes	NJ	no	dead	first	idiopathic	severe
yes	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol	severe
no	NJ	no	alive	recurrent	post ERCP	severe
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	first	idiopathic	severe
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	first	post ERCP	mild
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	Dama	first	idiopathic	severe
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	post ERCP	mild
no	NJ	yes	alive	first	alcohol	severe
no	oral	no	alive	first	post ERCP	mild
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	biliary	severe
no	oral	no	alive	first	biliary	severe
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	first	idiopathic	mild
no	NJ	no	alive	first	alcohol	severe
no	NJ	yes	alive	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	alcohol	mild
no	TPN	no	dead	first	drug-neomercozole	severe
no	NJ	no	Dama	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	recurrent	idiopathic	mild
no	oral	no	alive	recurrent	alcohol	mild
no	oral	no	alive	recurrent	idiopathic	mild
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	recurrent	idiopathic	mild
no	NJ	no	dead	first	biliary	severe
no	oral	no	alive	first	alcohol	mild
no	NJ	yes	dead	first	alcohol	severe
no	NJ	no	Dama	first	alcohol	severe
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	first	alcohol	severe

no	NJ	no	dama	first	biliary	severe
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	first	post ERCP	severe
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	recurrent	idiopathic	severe
no	nj	yes	alive	first	idiopathic	severe
no	NJ	no	alive	first	idiopathic	severe
no	nj	no	alive	first	alcohol	severe
no	NJ	no	alive	first	idiopathic	mild
no	oral	no	alive	first	idiopathic	mild
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	recurrent	biliary	mild
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	idiopathic	mild
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	biliary	severe
no	oral	no	alive	recurrent	idiopathic	mild
no	NJ	no	alive	first	alcohol	severe
no	oral	no	alive	first	post ERCP	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	alcohol	mild
yes	oral	no	dead	first	alcohol	severe
no	oral	no	alive	recurrent	idiopathic	mild
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	first	alcohol	mild
no	NJ	no	alive	first	idiopathic	severe
no	oral	no	alive	first	idiopathic	mild
no	NJ	no	alive	first	biliary	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	alcohol	mild
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	first	biliary	mild
no	oral	no	alive	recurrent	biliary	mild
no	NJ	no	dead	first	alcohol	severe
no	oral	no	alive	first	alcohol	mild
no	NJ	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	first	alcohol	mild
no	TPN	no	Dama	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	alcohol	mild
no	NJ	no	alive	recurrent	alcohol	severe
no	NJ	no	Dama	first	idiopathic	severe
no	NJ	no	alive	first	alcohol	severe
no	NJ	no	alive	recurrent	alcohol	mild
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	biliary	mild
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	first	idiopathic	mild
no	oral	no	alive	first	alcohol	mild
no	oral	no	alive	first	alcohol	severe

no	oral	no	alive	first	biliary	mild
no	NJ	no	alive	recurrent	biliary	severe
no	TPN	no	Dama	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	NJ	no	alive	first	alcohol	severe
no	oral	no	alive	first	biliary	mild
no	NJ	no	alive	first	idiopathic	mild
no	oral	no	alive	first	idiopathic	mild
no	NJ	no	alive	first	biliary	mild
no	NJ	no	alive	first	alcohol	severe
yes	NJ	no	alive	first	idiopathic	severe
no	oral	no	alive	first	alcohol	severe
no	oral	no	alive	recurrent	biliary	mild
no	oral	no	alive	recurrent	idiopathic	mild
yes	NJ	no	alive	first	alcohol	severe
no	oral	no	alive	first	alcohol	mild

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